Inhibitors of Cholesterol Biosynthesis. 1. 3,5-Dihydroxy-7-(*N*-imidazolyl)-6-heptenoates and -heptanoates, a Novel Series of HMG-CoA Reductase Inhibitors[1]

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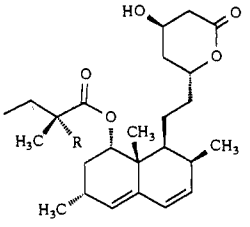
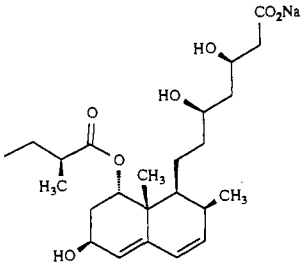
3,5-Dihydroxy-7-(*N*-imidazolyl)heptanoates **4** and the corresponding heptenoates **5** were synthesized as novel classes of potent HMG-CoA reductase (HMGR) inhibitors in which members of the latter series possess enzyme inhibitory activity greater than that of lovastatin **1** and pravastatin **2**. Structure–activity studies show that the 7-(*N*-imidazolyl)heptenoates **5** are more active than the corresponding heptanoates **4**. For both imidazolyl series, the 4-fluorophenyl group is preferred at C-5, and a broad range of aryl substituents which promote widely different lipophilicities is tolerated at C-4. While the CF_3 group is preferred at C-2 in the heptanoate series, the 2-(1-methylethyl) substituent is optimal in the heptenoate series. The 2-(1-methylethyl) and 5-(4-fluorophenyl) groups can be interchanged in the latter series as exemplified by **5ab**. Enzyme inhibitory activity resides principally in the 3*R*,5*S* series. These potent HMGR inhibitory activities by members of the heptenoate series translated well into whole cell activities in HepG2 cells. X-ray crystallographic studies on the active enantiomer **28** reveal noncoplanarity of the heptenoate C–C double bond with the imidazole ring; this finding provides an explanation for the high acid stability of the heptenoate series.

Hypercholesterolemia is a primary risk factor in coronary heart disease which is the major cause of death in the Western World.[2,3] Clinical studies with lipid lowering agents have established that lowering elevated serum cholesterol levels reduces the incidence of cardiovascular mortality.[3] In humans 70% of total body cholesterol is derived from *de novo* biosynthesis in the liver, and it has been established that one of the most effective approaches to lower serum cholesterol levels is by inhibiting its biosynthesis. The fungal metabolite lovastatin **1**, the microbially transformed product pravastatin **2**, and the semisynthetic analog, simvastatin **3**, are potent hypocholesterolemic agents[4] which are finding use in the clinic. This class of compounds inhibits 3-hydroxy-3-methylglutaryl CoA reductase (HMGR), a major rate limiting enzyme in cholesterol biosynthesis, and has been shown to induce the expression of hepatic low-density lipoprotein (LDL) receptors which mediate the clearance of LDL cholesterol from the plasma.



1 R = H
3 R = CH_3



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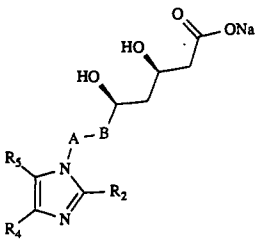
In designing structurally simplified analogs of these inhibitors, emphasis has focused on the replacement of the chiral decalin moiety.[5-7] These studies revealed that a wide range of achiral substituted cycloalkenyl,[5] aromatic,[6] and heteroaromatic[7] groups including the C-linked imidazolyl group[7g-i] could be incorporated while retaining good HMGR inhibitory activity. Herein we report the synthesis and biological activity of appropriately substituted 3,5-dihydroxy-7-(*N*-imidazolyl)heptanoates **4** and the corresponding heptenoates **5** as novel classes of highly



4 A-B = CH_2CH_2
5 A-B = (*E*)-CH=CH

active HMGR inhibitors in which members of the latter series possess enzyme inhibitory activity greater than lovastatin **1** and pravastatin **2**. In the accompanying paper,[8] we present a novel series of 3,5-dihydroxy-7-(*N*-pyrrolyl)-6-heptenoates with potent HMGR inhibitory activity.

Chemistry

Scheme I shows the convergent approach adopted for the synthesis of the heptanoate series. Wittig methylenation followed by oxidative hydroboration of aldehyde **6**[9] provided the homoalcohol **7**. Reaction of the anion of imidazole **8**[10] with the triflate of **7** at 0 °C yielded the coupled product **9**. Under these conditions, unsymmet-

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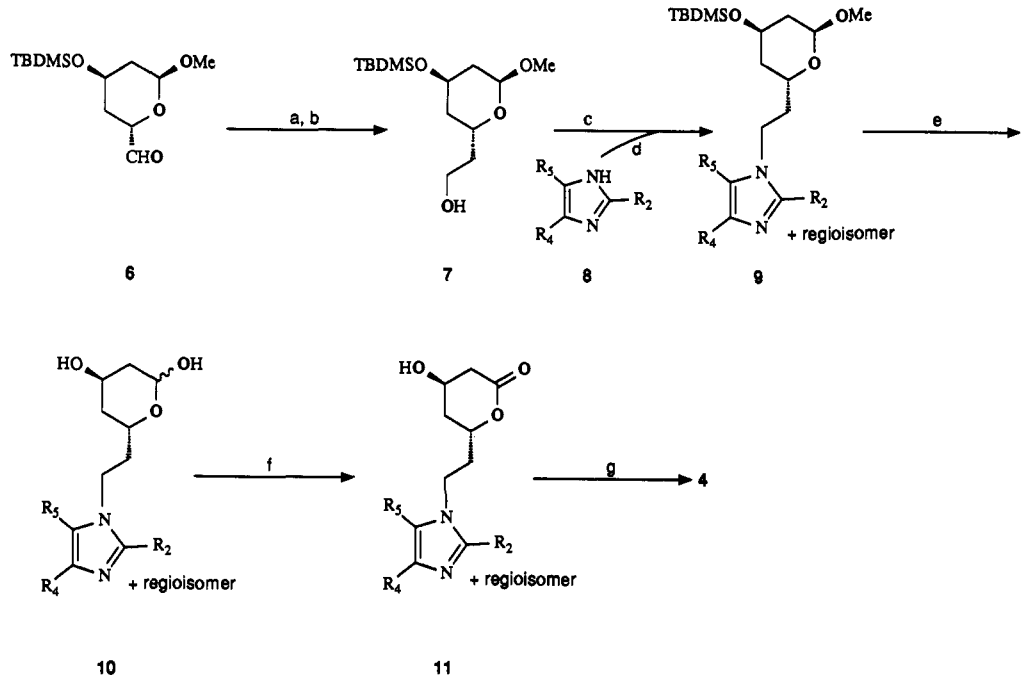
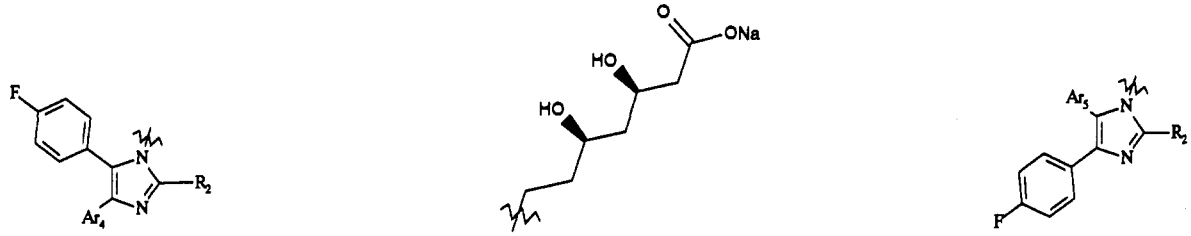
Scheme I[a]



[a] (a) $Ph_3P{=}CH_2$, THF; (b) 9-BBN, THF then 30% H_2O_2, aqueous NaOH; (c) Tf_2O, 2,6-lutidine, 0 °C; (d) $KN(TMS)_2$, THF; (e) TFA–H_2O–THF; (f) *N*-iodosuccinimide, TBAI, CH_2Cl_2, room temperature; (g) 1 equiv of 0.1 M aqueous NaOH. Regioisomers were separated by chromatographic methods at a convenient stage.

Table I. 3,5-Dihydroxy-7-(*N*-imidazoly)heptanoates **4**

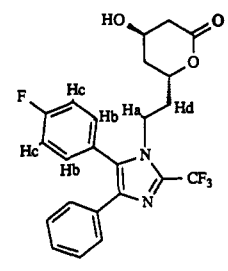


no.	R_2	Ar_4	molecular formula[a]	IC_{50}[b] (nM)	no.	R_2	Ar_5	molecular formula[a]	IC_{50}[b] (nM)
4a	CF_3	Ph	$C_{23}H_{21}F_4N_2NaO_4$	31	**4n**	CF_3	Ph	$C_{23}H_{21}F_4N_2NaO_4$	201
4b	CF_3	3-ClC_6H_4	$C_{23}H_{20}ClF_4N_2NaO_4$	17	**4o**	CF_3	3-ClC_6H_4	$C_{23}H_{20}ClF_4N_2NaO_4$[c]	41
4c	CF_3	3-MeC_6H_4	$C_{24}H_{23}F_4N_2NaO_4$	29	**4p**	CF_3	3-MeC_6H_4	$C_{24}H_{23}F_4N_2NaO_4$	74
4d	CF_3	3-$MeOC_6H_4$	$C_{24}H_{23}F_4N_2NaO_5$[c]	20	**4q**	CF_3	3-$MeOC_6H_4$	$C_{24}H_{23}F_4N_2NaO_5$[c]	135
4e	CF_3	4-FC_6H_4	$C_{23}H_{20}F_5N_2NaO_4$	38	**4e**	CF_3	4-FC_6H_4	$C_{23}H_{20}F_5N_2NaO_4$	38
4f	CF_3	4-MeC_6H_4	$C_{24}H_{23}F_4N_2NaO_4$	43	**4r**	CF_3	4-MeC_6H_4	$C_{24}H_{23}F_4N_2NaO_4$	750
4g	CF_3	4-$MeOC_6H_4$	$C_{24}H_{23}F_4N_2NaO_5$[c]	68	**4s**	CF_3	4-$MeOC_6H_4$	$C_{24}H_{23}F_4N_2NaO_5$[c]	418
4h	CF_3	4-$CF_3C_6H_4$	$C_{24}H_{20}F_7N_2NaO_4$	200	**4t**	CF_3	4-$CF_3C_6H_4$	$C_{24}H_{20}F_7N_2NaO_4$	>1000
4i	CF_3	3,5-$Me_2C_6H_3$	$C_{25}H_{25}F_4N_2NaO_4$	24	**4u**	CF_3	3,5-$Me_2C_6H_3$	$C_{25}H_{25}F_4N_2NaO_4$	38
4j	CF_3	3,5-Me_2-4-FC_6H_2	$C_{25}H_{24}F_5N_2NaO_4$	32	**4v**	CF_3	3,5-Me_2-4-FC_6H_2	$C_{25}H_{24}F_5N_2NaO_4$[d]	31
4k	CF_3	thien-2-yl	$C_{21}H_{19}F_4N_2NaO_4S$	64	**4w**	CF_3	thien-2-yl	$C_{21}H_{19}F_4N_2NaO_4S$	215
4l	CF_3	pyrid-3-yl	$C_{22}H_{20}F_4N_3NaO_4$[c]	66	**4x**	CF_3	pyrid-3-yl	$C_{22}H_{20}F_4N_3NaO_4$[c]	>1000
4m	Me_2CH	4-FC_6H_4	$C_{25}H_{27}F_2N_2NaO_4$[c]	316	**4m**	Me_2CH	4-FC_6H_4	$C_{25}H_{27}F_2N_2NaO_4$[c]	316

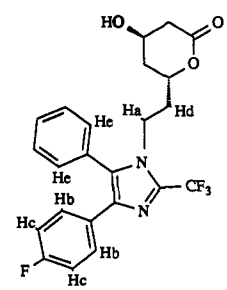
[a] Analytical results are within ±0.4% of theoretical values unless otherwise noted. [b] IC_{50} values were determined on at least two occasions with five dose levels of each inhibitor in duplicate and agreed within 15%. Pravastatin sodium salt was used as reference (5 nM; variation ±5%). See the Experimental Section for details. [c] Analytical data not obtained; correct high-resolution mass spectral data were obtained.[d] H: calcd, 5.28; found, 4.08.

rically substituted imidazoles **8** ($R_4 \neq R_5$) gave mixtures of N1- and N3-alkylated products which were separated by column chromatography or HPLC at a convenient stage. Deprotection of **9** with aqueous TFA followed by selective oxidation of the resultant lactol **10**, using *N*-iodosuccinimide and tetra *n*-butylammonium iodide,[11] afforded the lactone **11**; saponification provided the sodium salt **4** for biological testing.

The structure of regioisomers derived by alkylation of 4-(fluorophenyl)imidazoles was determined by NMR spectroscopy. For a regioisomeric pair **11a** and **11n** (see Tables I and II for definitions of these letters), triplets in

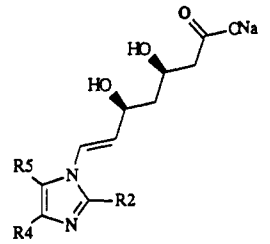


11a



11n

Table II. 3,5-Dihydroxy-7-(*N*-imidazolyl)heptenoates 5



no.	R_2	R_4	R_5	molecular formula[a]	IC_{50}[b] (nM) vs HMGR	IC_{50}[c] (nM) in HepG2 cells	log D[d]
5e	CF_3	4-FC_6H_4	4-FC_6H_4	$C_{23}H_{18}F_5N_2NaO_4$[e]	13	15.8	0.73
5m	Me_2CH	4-FC_6H_4	4-FC_6H_4	$C_{25}H_{25}F_2N_2NaO_4$[f]	2	5.3	0.72
5y	Me	4-FC_6H_4	4-FC_6H_4	$C_{23}H_{21}F_2N_2NaO_4$[e]	>100		
5z	Me_3C	4-FC_6H_4	4-FC_6H_4	$C_{26}H_{27}F_2N_2NaO_4$	7		
5aa	Me_2N	4-FC_6H_4	4-FC_6H_4	$C_{24}H_{24}F_2N_5NaO_4$[e]	9		
5ab	4-FC_6H_4	4-FC_6H_4	Me_2CH	$C_{25}H_{25}F_2N_2NaO_4$	1		0.83
5ac	Me_2CH	4-FC_6H_4	3-ClC_6H_4	$C_{25}H_{25}ClFN_2NaO_4$[g]	8		
5ad	Me_2CH	4-FC_6H_4	3,5-$Cl_2C_6H_3$	$C_{25}H_{24}Cl_2FN_2NaO_4$[e]	22		
5ae	Me_2CH	4-FC_6H_4	3,5-$Me_2C_6H_3$	$C_{27}H_{30}FN_2NaO_4$[e]	56		
5af	Me_2CH	4-FC_6H_4	2-Me-4-FC_6H_3	$C_{26}H_{27}F_2N_2NaO_4$	4		0.86
5ag	Me_2CH	4-FC_6H_4	3,5-Me_2-4-FC_6H_2	$C_{27}H_{28}F_2N_2NaO_4$[e]	30		
5ah	Me_2CH	4-FC_6H_4	3,5-Et_2-4-FC_6H_2	$C_{29}H_{33}F_2N_2NaO_4$[h]	100		
5ai	Me_2CH	3,5-Me_2-4-ClC_6H_2	4-FC_6H_4	$C_{27}H_{29}ClFN_2NaO_4$	2	0.9	2.27
5aj	Me_2CH	pyrid-3-yl	4-FC_6H_4	$C_{24}H_{25}FN_3NaO_4$	1		−0.43
5ak	Me_2CH	3-$MeSO_2C_6H_4$	4-FC_6H_4	$C_{26}H_{28}FN_2NaO_6S$[e]	2		−0.60
5al	Me_2CH	3-$MeNHC_6H_4$	4-FC_6H_4	$C_{26}H_{28}FN_3NaO_4$[e]	3		−0.05
28	Me_2CH	4-FC_6H_4	4-FC_6H_4	$C_{25}H_{28}F_2N_2O_4$[f]	1	2.5	
30	Me_2CH	4-FC_6H_4	4-FC_6H_4	$C_{25}H_{28}F_2N_2O_4$[f]	nd[i]		
31	Me_2CH	4-FC_6H_4	4-FC_6H_4	$C_{25}H_{28}F_2N_2O_4$[f]	700		
32	Me_2CH	4-FC_6H_4	4-FC_6H_4	$C_{25}H_{28}F_2N_2O_4$[f]	2000		
1	lovastatin[j]				3	7	
2	pravastatin				5	452	
35					2.6[k]		

[a] Analytical results are within ±0.4% of theoretical values unless otherwise noted. [b] IC_{50} values were determined on at least two occasions with five dose levels of each inhibitor in duplicate and agreed within 15%. Pravastatin sodium salt was used as reference (5 nM; variation ±5%). See the Experimental Section for details. [c] IC_{50} values were determined twice with at least 5 inhibitor concentrations in triplicate and agreed within 15%. Lovastatin sodium salt was used as standard. [d] log D was measured in *n*-octanol–water system in which the compound was dissolved in pH 7.4 aqueous borax–phosphate buffer saturated with *n*-octanol and eluted through a column of *n*-octanol physically bonded to fractionated hyflosupercel in a HPLC system. [e] Analytical data exceeded error limit; high-resolution mass spectral data were obtained. [f] Analytical data were obtained for the free acids. [g] N: calcd, 5.02; found, 4.55. [h] H: calcd, 6.88; found, 5.66. [i] nd = not determined. [j] Sodium salt of the corresponding dihydroxy acid was used. [k] Data from ref 7g.

the ^1H NMR spectrum[12] for each compound assigned to the protons ortho (Hc) to the fluorine of the 4-fluorophenyl ring resonated at δ 7.40 and 7.06 ppm. NOE[13a] experiments on the isomer having Hc resonating at 7.40 ppm showed signal enhancement to the Hb protons upon irradiation of Ha or Hd. Rotating Overhauser enhancement spectroscopy[13b] (ROESY) on the other isomer having Hc resonating at 7.06 ppm showed enhancements between Ha or Hd and He. Therefore Hc in 4-(4-fluorophenyl)-imidazole **11n** and 5-(4-fluorophenyl)imidazole **11a** resonate at 7.06 and 7.40 ppm, respectively. For pairs of N1- and N3-alkylated regioisomers a $\Delta\delta \approx 0.3$ ppm for the Hc protons was consistently observed. Compounds in which the Hc proton resonates at a lower value were therefore assigned as the 4-(4-fluorophenyl)imidazole isomers (*vide infra*).

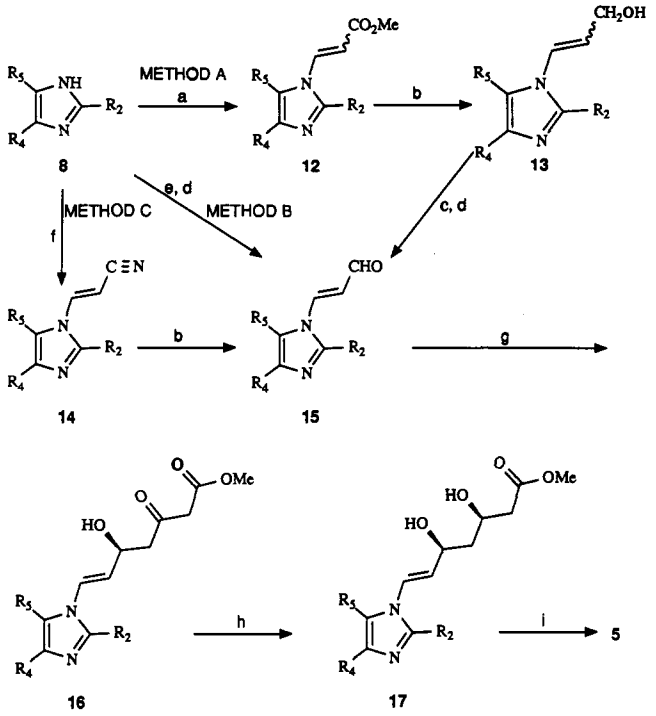
Our approach to the heptenoate series is shown in Scheme II. Three routes to the key intermediate vinylogous aldehyde **15** were established. Unsymmetrically substituted imidazoles 8 ($R_4 \neq R_5$) gave mixtures of N1- and N3-alkylated products which were separated at a convenient stage. In method A,[14] alkylation of the appropriately substituted imidazole 8 with methyl propiolate gave the unsaturated ester **12** as a mixture of geometrical isomers which, if desired, could be separated by column chromatography. DIBAL-*H* reduction of **12** provided the allylic alcohol **13**, manganese dioxide oxidation of which followed by iodine-induced double bond isomerization afforded the (*E*)-aldehyde **15**. Direct coupling of 8 with propiolaldehyde followed by double bond isomerization with iodine also yielded the aldehyde **15** (method B). Neither method was applicable to the highly electron-deficient 2-(trifluoromethyl)imidazole **8e** (R_2 = CF_3), (see Tables I and II for definitions of these letters). In this series, however, base-induced alkylation of **8e** with 2,3-dibromopropionitrile in DMF gave exclusively the (*E*)-isomer of the unsaturated nitrile **14e**, DIBAL-*H* reduction of which followed by aqueous workup yielded the aldehyde **15e** (method C). This method was used exclusively with 2-(trifluoromethyl)imidazole **8e** (R_2= CF_3); no reaction occurred with 2-isopropylimidazoles (**8**, R_2 = *i*-Pr).

In the case of 4-(3-pyridyl)imidazole **8aj** (see Tables I and II for the definitions of these letters), the corresponding pyridine *N*-oxide was prepared (MCPBA) and used in the alkylation step in order to avoid competitive side reactions. The derived unsaturated ester **12** was reduced in one pot with DIBAL-*H* to the allylic alcohol **13aj**.

Condensation of the vinylogous aldehyde **15** with the dianion of methyl acetoacetate afforded the aldol product **16**. Stereoselective reduction[15] using *in situ* generated methoxydiethylborane and sodium borohydride in tetrahydrofuran–methanol at −78 °C gave the *syn*-diol **17**; saponification yielded the sodium salt **5**.

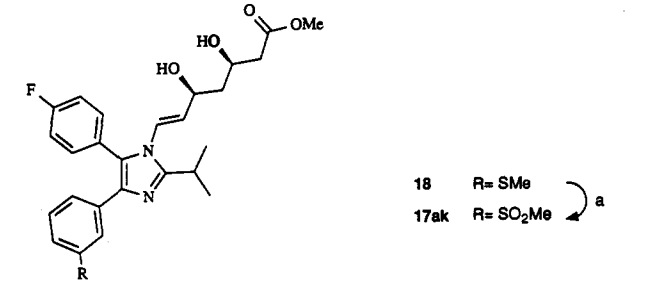
Modifications to the established route were adopted for the synthesis of methylsulfonyl and methylamino derivatives **5ak** and **5al** respectively. Sulfone **5ak** was syn-

Scheme II[a]



[a] (a) $CH{\equiv}CCO_2Me$, THF, Δ; (b) DIBAL, CH_2Cl_2, −78 °C → 0 °C; (c) MnO_2, CH_2Cl_2, room temperature; (d) I_2, CCl_4, N_2, Δ; (e) $CH{\equiv}CCHO$, Δ; (f) $BrCH_2CH(Br)CN$, K_2CO_3, Et_3N, DMF, 3 d, room temperature; (g) NaH, *n*-BuLi, $MeCOCH_2CO_2Me$, THF, 0 °C; (h) Et_3B, MeOH, $NaBH_4$, THF, −78 °C; (i) 1 equiv of 0.1 M aqueous NaOH. Regioisomers were separated at a convenient stage.

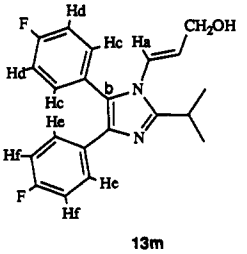
Scheme III[a]



[a] (a) 30% aqueous H_2O_2, SeO_2, MeOH, room temperature. See Scheme II for the preparation of 18.

thesized from the sulfide **18** (prepared via method A) by oxidation with 30% aqueous hydrogen peroxide–selenium(IV) oxide in methanol[16] (Scheme III) followed by saponification of the derived sulfone **17ak**. For the synthesis of the methylamino derivative **5al**, the protected 4-(3-aminophenyl)imidazole **22** was prepared as outlined in Scheme IV. Elaboration of **22** using method A followed by deprotection of the derived diol ester **23** gave **5al**.

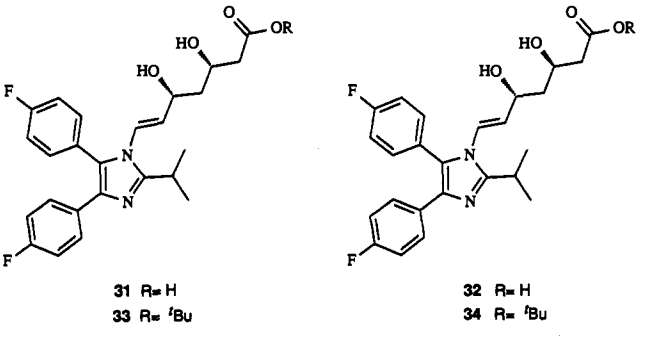
Unambiguous assignment of N1- and N3-alkylated products in nonsymmetrically substituted imidazoles possessing a 4-fluorophenyl substituent was made possible following NMR studies on **13m**. Thus, heteronuclear



multiple bond correlation[17] studies (HMBC), optimized for 5-Hz coupling, using the inverse method showed correlations of carbon b (125.7 ppm) with protons Ha (6.62, d) and Hc (7.25, dd). ROESY spectroscopy showed no signal enhancement between the vinyl and aromatic protons but established that Hc was adjacent to Hd (7.1, t) and that He (7.4, dd) was adjacent to Hf (6.9, t). These studies confirmed that the 3 and 5 protons of the 4-(4-fluorophenyl) ring resonate at lower δ value (*ca.* 6.9, t) compared with the corresponding protons in the 5-(4-fluorophenyl) ring (7.1, t). These findings were consistently observed for pairs of N1- and N3-alkylated isomers and compounds in which the 3 and 5 protons of the 4-fluorophenyl ring resonate at a lower value were assigned to the 4-(4-fluorophenyl)imidazole series (*vide supra*).

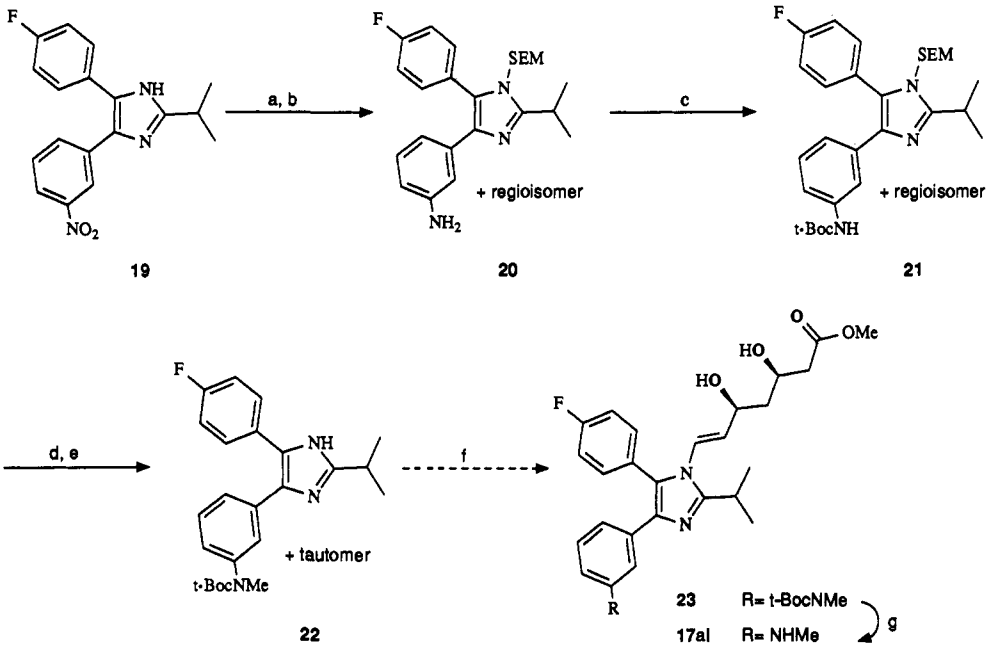
In the 5-(4-fluoro-2-methylphenyl)imidazolyl series, the intermediate esters **16af** and **17af** together with the derived sodium salt **5af** were each isolated as a 1:1 mixture of two components. As N1 and N3 regioisomers were separated at the aldehyde stage (**15af**), these two components were assigned as rotamers due to restricted rotation of the 2-substituted phenyl ring attached to the 5-position of the 1,2,4,5-tetrasubstituted imidazole. Confirmation of this was established by high temperature ^{1}H-NMR studies on **5af** which caused coalescence of the two sets of signals at 135 °C in d_6-DMSO.

Asymmetric aldol condensation[18] was employed in the syntheses of chiral acids **28** and **30** (Scheme V). Condensation of **15m** with the dianion of (*S*)-2-acetoxy-1,1,2-triphenylethanol, generated with 2 equiv of lithium dicyclohexylamide, in THF at −40 °C gave the aldol product **24** in 94% yield and high diastereofacial selectivity (86% de). Transesterification followed by Claisen condensation of the resultant methyl ester **25** with lithiated *tert*-butyl acetate afforded, after crystallization, the 5*S* hydroxy ketoester **26** in which none of the other enantiomer was detected by chiral HPLC (see the Experimental Section). Stereoselective reduction[15] using *in situ* generated methoxydiethylborane and sodium borohydride in tetrahydrofuran–methanol at −78 °C gave, after crystallization, the *syn*-diol ester **27** (*syn*:*anti* > 99:1 by HPLC) in 60% yield. Hydrolysis yielded the crystalline 3*R*,5*S* acid **28** (99% ee). Triacetoxyborohydride reduction[19] of **26** gave, after crystallization, the *anti*-diol ester **29** in good yield (83%) and high diastereoselectivity (*anti*:*syn* 96.4:3.6 by HPLC); hydrolysis yielded the 3*S*,5*S* acid **30**. The (3*S*,5*R*) and (3*R*,5*R*) enantiomers **31** and **32** were similarly prepared using (*R*)-2-acetoxy-1,1,2-triphenylethanol.



Single-crystal X-ray crystallography (Figure 1) confirmed the 3*R*,5*S* absolute stereochemistry of the more potent enantiomer **28**. The torsional angle between the heptenoate carbon–carbon double bond and imidazole ring is 59.3° (atoms C6, C7, N8, C12). Those between the

Scheme IV[a]



[a] (a) KN(TMS)$_2$, SEMCl, THF, −78 °C → room temperature; (b) $NaBH_4$, S_8, THF, room temperature, 18 h, Δ 2.5 h; (c) (t-Boc)$_2$O, Na_2CO_3, dioxan, room temperature; (d) NaH, MeI, DMF, room temperature, 3 h; (e) TBAF, THF, Δ, 5 h; (f) see Scheme II and text; (g) TFA, anisole, 0 °C.

imidazole ring and the 5-(4-fluorophenyl) and 4-(4-fluorophenyl) rings are 68.78° (atoms N8, C12, C13, C14) and 32.71° (atoms C12, C11, C19, C24), respectively. This lack of coplanarity between the imidazole ring and the heptenoate carbon–carbon double bond explains the high acid stability of these compounds in which **5m** was recovered after 3 days at 37 °C in pH 2 buffer.[20] It is interesting to note that C-linked biphenyl and indolyl derivatives are known to undergo acid-catalyzed decomposition.[21]

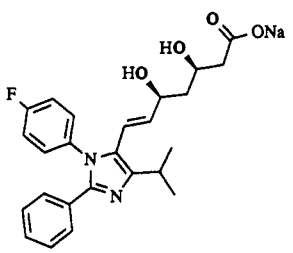
Biological Results and Discussion

The sodium dihydroxycarboxylates listed in Tables I and II were evaluated for inhibitory activity against washed rat liver microsomal HMGR using a published procedure[22] modified as described in the Experimental Section. Selected 7-(*N*-imidazolyl)heptenoates **5** were also tested for their ability to inhibit cholesterol biosynthesis in HepG2 cells.

A general comparison of the activity data contained in Tables I and II immediately reveals that the 7-(*N*-imidazolyl)heptenoates are more active than the corresponding heptanoates.[23] Within the heptanoate series, Table I, replacement of the 1-methylethyl substituent at C-2 by CF_3 resulted in a considerable increase in potency as illustrated by activity associated with **4e** when compared with that for **4m**. Incorporation of a wide range of substituted phenyl groups and heteroaryl substituents at C-4 provides compounds with equivalent enzyme inhibitory activities (**4a–4g, 4i–4l**). The preferred structural features at C-5 are more narrowly defined; phenyl groups incorporating *p*-fluoro (**4e**), *m*-chloro (**4o**), and *m*-methyl (**4p, 4u, 4v**) substituents promote good enzyme inhibitory activity.

In agreement with literature findings,[7b,u] optimal activity resides in compounds possessing the 2-(1-methylethyl) substituent (compare **5m** with **5e, 5y, 5z, 5aa**) in the 7-(*N*-imidazolyl)heptenoate series, Table II, and SAR derived from modifications to the substituents at C-4 and C-5 largely paralleled those found in the heptanoate series.

The (4-fluorophenyl) group is preferred at C-5, and when this group is retained potent HMGR inhibitory activity is observed when aryl groups which confer widely different lipophilicities were incorporated at C-4 (**5m, 5ai, 5aj, 5ak, 5al**). Potent activity was retained when the 2-(1-methylethyl) group and a 5-(4-fluorophenyl) group were interchanged as in **5ab**. In accordance with previous studies,[6d] enzyme inhibitory activity resided principally in the (3*R*,5*S*) enantiomer **28**. Members of the 7-(*N*-imidazolyl)heptenoate series (**5m, 5ab, 5ai, 5aj, 5ak, 28**) are more potent than lovastatin **1** and pravastatin **2**. The C-linked imidazolylheptenoate **35** is reported to possess IC_{50} of 2.6 nM.[7g]



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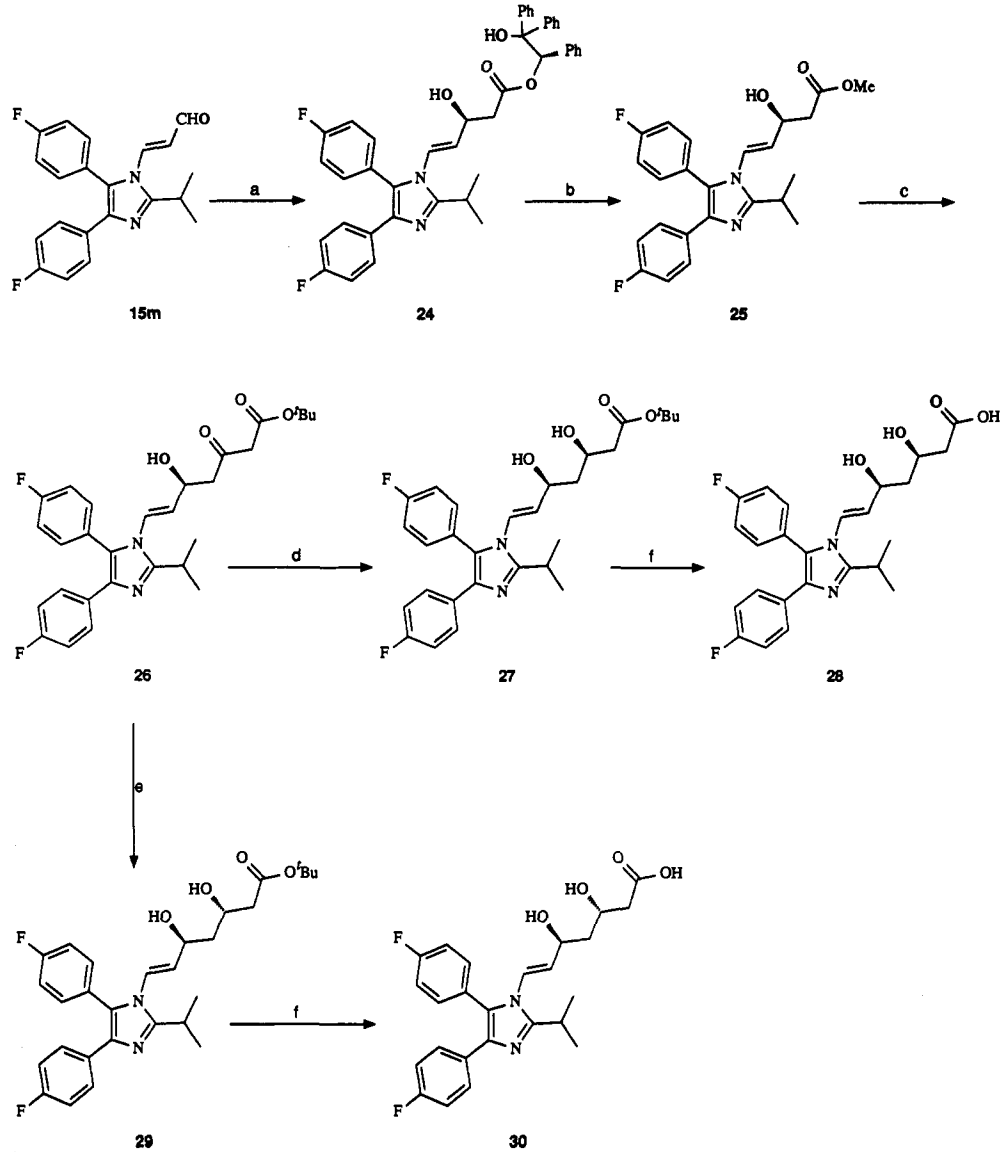
Selected compounds were investigated for their ability to inhibit the incorporation of [^{14}C]acetate into cholesterol in HepG2 cells (Table II). The HMGR IC_{50} values of **5e, 5m, 5ai,** and **28** translated well into whole cell activities. Indeed **5ai** (IC_{50} = 0.9 nM) and **28** (IC_{50} = 2.5 nM) are more potent than lovastatin **1** in HepG2 cells; pravastatin **2** is considerably less active in this system as has been reported previously.[24] Similar rat hepatocyte studies using [^{14}C]acetate showed potent inhibition of cholesterol biosynthesis by **5m** (IC_{50} = 1.5 nM). However using [^{3}H]-mevalonolactone (which labels the cholesterol biosynthesis pathway beyond HMGR) **5m** did not inhibit incorporation of this label into cholesterol at 100 nM (data not shown). Thus this compound does not significantly inhibit the

Scheme V[a]



[a] (a) LiN(c-hex)$_2$, (*S*)-2-acetoxy-1,1,2-triphenylethanol,[18] THF, −40 °C; (b) NaOMe, MeOH; (c) *n*-BuLi, i-Pr$_2$NH, t-BuOAc; (d) Et$_3$B, MeOH, NaBH$_4$, THF, −78 °C; (e) NaBH$_4$ or Me$_4$NBH$_4$, AcOH, 15 → 20 °C; (f) aqueous NaOH and then 2 N aqueous HCl to pH 4.

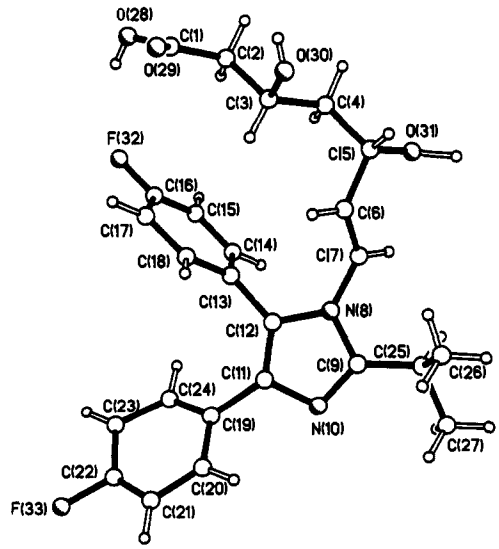


Figure 1. X-ray crystallographic structure of **28**.

microsomal conversion of mevalonate to cholesterol, confirming the site of action of **5m** to one of the early steps of the biosynthetic pathway.

Conclusion

3,5-Dihydroxy-7-(*N*-imidazolyl)heptanoates **4** and the corresponding heptenoates **5** have been synthesized and shown to inhibit HMGR. The heptenoate series is more active than the corresponding heptanoate series. Members of the former series have been shown to possess more potent HMGR inhibitory activity than lovastatin **1** and pravastatin **2**. At the C-2 position of the imidazole ring, CF_3 is preferred in the heptanoate series but 2-(1-methylethyl) is optimal in the heptenoate series. In the latter series, the 2-(1-methylethyl) and 5-(4-fluorophenyl) substituents can be interchanged without loss of activity. SAR at C-4 and C-5 of the imidazolyl system are similar in both series. Retaining the preferred 4-fluorophenyl group at C-5 in the heptenoate series, potent HMGR inhibitory activity is observed when aryl groups are incorporated at C-4 which promote widely different lipophilicities. The inhibitory activity of the heptenoate series resides principally in the 3*R*,5*S* series. These potent HMGR inhibitory activities by members of the heptenoate series translated well into whole cell activities in HepG2 cells. X-ray crystallography of **28** shows the lack of coplanarity between the heptenoate C–C double bond and the imidazole ring; this finding

provides an explanation for the high acid stability of the heptenoate series.

Experimental Section

Dry tetrahydrofuran was obtained by distillation from potassium or sodium ketyl of benzophenone under nitrogen. Dry dichloromethane and dimethylformamide were obtained by distillation from calcium hydride and stored over 4-Å molecular sieves under nitrogen. Dry methanol was obtained by distillation from magnesium turnings and stored over 4-Å molecular sieves under nitrogen. Unless otherwise noted, all reagents were purchased commercially and used without purification. Organic solutions were dried over $MgSO_4$, and column chromatography was performed on silica gel 60 (Merck, Art. No. 7734 or 9385). R_f values were determined on TLC plates precoated with 0.25-mm-thick silica gel 60 F_{254} (Merck, Art. No. 5714) with appropriate solvent systems and were visualised with UV light, 5% phosphomolybdic acid in 95% ethanol, or *p*-anisaldehyde in ethanol–sulfuric acid–acetic acid. Melting points were determined on a Reichert apparatus and are uncorrected. UV spectra were recorded on a Nicolet 55XC FT IR spectrophotometer. NMR spectra were recorded on a Varian XL 200, Bruker AM 250 or Varian VXR 400 spectrometer using TMS as internal standard. Accurate masses were determined by high-resolution -ve FAB mass spectrometry performed on a Kratos Concept 1H mass spectrometer. Elemental analyses were determined with a Perkin-Elmer 240C or a Carlo-Erba 1106 elemental analyzer. Optical rotations were measured on an Optical Activity Ltd type-AA-10 polarimeter. Unless otherwise stated, chiral HPLC was performed on an Enantiopac AGP 100-mm × 4.6-mm column using 0.02 M sodium dihydrogen phosphate pH 4 buffer containing up to 3% isopropyl alcohol as eluant. Routine HPLC was performed on a spherisorb ODS-2 column using 0.05 M aqueous ammonium acetate–acetonitrile as mobile phase.

Biological Methods. Enzyme Preparation. A rat liver microsomal preparation of HMGR was obtained from male Wistar rats. The animals were housed in a light-controlled room where the dark period was from 0200 to 1400 h and they had free access to normal chow and water.

Rats (100–120 g) were killed at 0800 h, the diurnal high of HMGR activity. Livers were removed and placed in ice-cold buffer A (50 mM potassium phosphate, pH 7.4 containing 250 mM NaCl, 10 mM EDTA, 1 mM dithiothreitol). The livers were chopped with scissors and washed to remove blood. Sufficient buffer A was added to give a 20% (w/v) homogenate, and the livers were homogenized in a precooled Potter–Elvehjem homogenizer using 6 strokes of a motor driven Teflon pestle.

The homogenate was centrifuged at 10000*g* for 30 min. The resulting supernatant was removed *via* a pipette in order not to disturb the mitochondria-rich pellet and centrifuged at 105000*g* for 1 h. The supernatant was removed, and the pellets were washed and resuspended in buffer A using a hand-held homogenizer and then respun. All of the above procedures were carried out at 4 °C. The final pellets were resuspended in buffer A at a protein concentration of 10–20 mg/mL, stored in 100-μL aliquots at −70 °C, and used within a month.

Assay Conditions. This is a modification of the procedure reported by Shapiro *et al.*[22] Assays were conducted in buffer A. Enzyme plus inhibitor (50 μL) were preincubated at 37 °C for 10 min followed by the addition of 25 μL of cofactor/substrate solution containing 2.25 mol of glucose 6-phosphate, 0.15 I.U. of glucose 6-phosphate dehydrogenase, 225 nmol of $NADP^+$, and 2.5 nmol of DL-3-(hydroxymethyl)-[3-^{14}C]glutaryl CoA (sp. act. 1.92 GBq/mmol).

The reaction was carried out within the linear range for time and protein and terminated by the addition of HCl (2.5 M, 10 μL). Following lactonization for 30 min at 37 °C, the samples were centrifuged in a Microfuge to sediment denatured protein. An aliquot (50 μL) of supernatant was added to 450 μL of buffer B (55 mM sodium acetate/acetic acid, pH 4.6) and applied to a 3-mL AG 1-X4 (200–400 mesh) chloride form anion-exchange column (Bio-Rad). Labeled mevalonate was eluted directly into scintillation vials with 2.5 mL of buffer C (buffer B containing 50 mM NaCl). Scintillation fluid (Packard Pico-Aqua, 10 mL) was then added to each vial. In preliminary validation experiments a standard sample of *R,S*-[2-^{14}C]mevalonolactone was carried through the column chromatography. Recoveries were >94%. Compounds were tested for their inhibitory characteristics at five concentrations, in duplicate. Assays were performed on at least two occasions and IC_{50} values agreed within 15%.

Inhibition of Acetate Incorporation into Cholesterol in HepG2 Cells. Cells were maintained in modified Minimum Essential Eagles Medium (MEM) supplemented with 10% fetal calf serum and grown to 80% confluency. The medium was changed to serum-free MEM prior to incubation with test compounds. Inhibitor and sodium [^{14}C]acetate were added simultaneously, and the incubation continued for 3 h. The mixture was saponified and extracted with petroleum ether. Evaporation of organic solution under a stream of nitrogen gave a residue which was dissolved in methanol/propan-2-ol (1:1, v/v). [^{14}C]Cholesterol was separated by HPLC (Spherisorb 5-μm ODS-2 column eluted with methanol/propan-2-ol, 4:1, v/v) and quantified using Betacord 1208 radioactivity monitor with a 0.5-mL flow cell after mixing the column eluant with Optiphase Safe scintillant (LKB). Incubations were performed twice in triplicate with at least five inhibitor concentrations, and IC_{50} values agreed within 15%.

2-[4β-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2β-methoxytetrahydro-2*H*-pyran-6α-yl]ethan-1-ol (7). To a stirred suspension of methyltriphenylphosphonium bromide (23.72 g, 66.30 mmol) in dry THF (500 mL) at 0 °C under nitrogen was added *n*-butyllithium (1.6 M in hexanes, 14.6 mL) dropwise over 10 min. The resultant solution was stirred for a further 0.3 h at 0 °C. A solution of **6**[9] (13.99 g, 50.98 mmol) in dry THF (50 mL) was added dropwise over 5 min, and then the mixture was stirred at 0 °C for a further 2 h. The reaction was quenched with acetone, and then the mixture was evaporated to dryness to give a purple solid. This was chromatographed on silica gel eluting with ethyl acetate–hexane (1:9) to give a pale yellow oil (10.79 g).

To a solution of this oil (5.0 g, 18.35 mmol) in dry THF (180 mL) at 0 °C under nitrogen was added gradually a THF solution of 9-BBN (0.5 M, 112 mL), keeping the temperature below 3 °C. The mixture was stirred at 0 °C for 3 h and then at 20 °C for 18 h. After the mixture was cooled to 0 °C, water (10 mL) was added followed, when effervescence had subsided, by aqueous sodium hydroxide (3 M, 22.3 mL) and then 30% aqueous hydrogen peroxide (26.8 mL), keeping the temperature below 50 °C. After the addition the mixture was heated at 50 °C for 3.5 h, cooled, and saturated with solid potassium carbonate. The mixture was filtered, and the filtrate was extracted with ethyl acetate (2 × 250 mL). The combined extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel using gradient elution with ethyl acetate–cyclohexane (1:10 to 3:10) to give **7** (5.34 g, 82%) as a pale yellow oil: NMR ($CDCl_3$) δ 0.03, 0.05 (2 s, 6H), 0.85 (s, 9H), 1.80 (m, 6H), 2.68 (m, 1H), 3.30 (s, 3H), 3.79 (m, 2H), 4.03 (m, 1H), 4.31 (m, 1H), 4.68 (m, 1H). Anal. ($C_{14}H_{30}O_4Si$) C, H.

1-[2-[4β-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2β-methoxytetrahydro-2*H*-pyran-6α-yl]ethyl]-5-(4-fluorophenyl)-4-phenyl-2-(trifluoromethyl)-1*H*-imidazole (9a) and the Corresponding N3-Alkylated Isomer (9n). 5-(4-Fluorophenyl)-4-phenyl-2-(trifluoromethyl)-1*H*-imidazole[10] **8a** (1.50 g, 4.90 mmol) was dissolved in dry THF (30 mL), and the resultant solution was cooled to −20 °C under nitrogen. A THF solution of sodium bis(trimethylsilyl)amide (0.5 M, 12.5 mL) was added dropwise with stirring to afford a solution of the imidazole anion which was stored at −20 °C. Trifluoromethanesulfonic anhydride (1.0 mL, 6.06 mmol) was added dropwise to a stirred solution of **7** (1.50 g, 5.16 mmol) and dry pyridine (0.93 mL, 11.40 mmol) in dry dichloromethane (20 mL) under nitrogen at −20 °C. After 0.5 h hexane (20 mL) cooled to −20 °C was added, and the suspension was stirred vigorously at −20 °C for 10 min before centrifugation. The supernatant liquid was set aside at −20 °C while the solid was washed with cold hexane as before, centrifuged, and the supernatant liquid separated. To the combined hexane solutions stirred at −20 °C was added dropwise the mixture containing the previously prepared imidazole anion. After 9 min at −20 °C the mixture was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:8) to give a mixture of **9a** and **9n** (1.80 g, 60%) as a light brown gum: NMR (d_6-DMSO) δ 0.88 (s, 9H), 3.18 and 3.20 (2 s, 3H), 4.54 (m, 1H), 6.90 (t, 1H, J = 9 Hz), 7.15–7.55 (m, 9H); MS ($C_{30}H_{39}F_4N_2O_3Si$) calcd 579.2666, found 579.2680.

[2αβ,4β]-6α-[2-[5-(4-Fluorophenyl)-4-phenyl-2-(trifluoromethyl)-1*H*-imidazol-1-yl]ethyl]tetrahydro-2*H*-pyran-2,4-diol (10a) and the Corresponding N3-Alkylated Isomer (10n). A mixture of **9a** and **9n** (0.15 g, 0.26 mmol) in trifluoroacetic acid–THF–water (3:2:2, 7 mL) was stirred at 20 °C for 2.5 h. The reaction mixture was diluted with ether (20 mL) and neutralized with saturated aqueous sodium bicarbonate. The organic phase was washed with water, dried, and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (2:1) to afford a mixture of **10a** and **10n** (0.027 g, 23%): NMR ($CDCl_3$) δ 2.50, 2.68, 2.89 (3 m, 1H), 3.60–4.30 (m, 4H), 4.82, 4.97, 5.18 (3 m, 1H), 6.80–7.60 (m, 9H). Anal. ($C_{23}H_{22}F_4N_2O_3$) C, H, N.

***trans*-6-[2-[5-(4-Fluorophenyl)-4-phenyl-2-(trifluoromethyl)-1*H*-imidazol-1-yl]ethyl]-4-hydroxytetrahydro-2*H*-pyran-2-one (11a) and the Corresponding N3-Alkylated Isomer (11n).** A mixture of **10a** and **10n** (0.052 g, 0.12 mmol) in dichloromethane (2 mL) was added to a solution of *N*-iodosuccinimide (0.078 g, 0.35 mmol) and tetra-*n*-butylammonium iodide (0.043 g, 0.12 mmol) in dichloromethane (4 mL). The mixture was stirred in the dark for 2.5 h, diluted with dichloromethane, washed twice with water, dried, and evaporated. The residual oil was chromatographed on silica gel plates eluting with ethyl acetate–hexane (3:1) to afford **11a** (0.017 g, 31%) which crystallized from diethyl ether to give white crystals: mp 176–178 °C; R_f 0.53 (SiO_2/ethyl acetate–hexane, 3:1); NMR (d_6-DMSO) δ 1.50–1.63 (m, 2H), 1.76–1.86 (m, 2H), 2.32 (dd, 1H, *J* = 16.5 and 2.5 Hz), 2.58 (dd, 1H, *J* = 16.5 and 5.5 Hz), 3.97–4.06 (m, 2H), 4.11–4.18 (m, 2H), 4.40–4.49 (m, 1H), 5.10–5.16 (br s, 1H), 7.16–7.28 (m, 3H), 7.34 (d, 2H, *J* = 6.5 Hz), 7.40 (t, 2H, *J* = 8.5 Hz), 7.57 (dd, 2H, *J* = 8.5 and 6 Hz). Anal. ($C_{23}H_{20}F_4N_2O_3$) C, H, N. Further elution gave **11n** (0.024 g, 44%) which was crystallized from THF–hexane to give colorless crystals: mp 152–154 °C; R_f 0.43 (SiO_2/ethyl acetate–hexane, 3:1); NMR (d_6-DMSO) δ 1.48–1.60 (m, 2H), 1.75–1.90 (m, 2H), 2.29 (dd, 1H, *J* = 16.5 and 3 Hz), 2.56 (dd, 1H, *J* = 16.5 and 5 Hz), 3.97–4.04 (m, 2H), 4.11–4.19 (m, 1H), 4.39–4.48 (m, 1H), 4.8–5.2 (br s, 1H), 7.06 (t, 2H, *J* = 8 Hz), 7.36 (dd, 2H, *J* = 8 and 6 Hz), 7.49–7.53 (m, 2H), 7.56–7.62 (m, 3H).

(±)-*erythro*-3,5-Dihydroxy-7-[5-(4-fluorophenyl)-4-phenyl-2-(trifluoromethyl)-1*H*-imidazol-1-yl]heptanoic Acid, Sodium Salt (4a). To a stirred solution of **11a** (0.014 g, 0.031 mmol) in THF (3 mL) was added aqueous sodium hydroxide (0.1 M, 0.35 mL). The mixture was evaporated, taken up in water, washed twice with ether, and freeze-dried to give **4a** (0.015 g, 99%) as a brown solid: NMR (D_2O) δ 1.30–2.00 (m, 4H), 2.28 (m, 2H), 3.86 (m, 1H), 4.12 (m, 2H), 7.10–7.50 (m, 9H). Anal. (free acid, $C_{23}H_{22}F_4N_2O_4$) C, N; H: calcd, 4.76; found, 5.17.

General Procedures for the Preparation of Vinylogous Aldehyde 15. Method A. (*E*) 3-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-2-propenoic Acid, Methyl Ester (12m). A mixture of 4,5-bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazole[10] **8m** (2.00 g, 6.7 mmol) and methyl propiolate (2.55 g, 30.4 mmol) in dry THF (40 mL) was heated at reflux under nitrogen for 65 h. The reaction mixture was allowed to cool to room temperature and then purified by flash column chromatography on a silica gel column. Elution of the column with ethyl acetate–cyclohexane (3:17) gave the *trans*-**12m** (1.02 g, 40%): IR ($CHBr_3$) 1713, 1643, 1513, 1250, 1226 cm^{-1}; UV λ_{max} 248.4 (ε 22 180) nm in methanol; NMR ($CDCl_3$) δ 1.46 (d, 6H, *J* = 7.5 Hz), 3.24 (septet, 1H, *J* = 7.5 Hz), 3.72 (s, 3H), 5.29 (d, 1H, *J* = 15 Hz), 6.91 (t, 2H, *J* = 9 Hz), 7.18 (t, 2H, *J* = 9 Hz), 7.31 (dd, 2H, *J* = 9 and 6 Hz), 7.40 (dd, 2H, *J* = 9 and 6 Hz), 7.80 (d, 1H, *J* = 15 Hz). Anal. ($C_{22}H_{20}F_2N_2O_2$) C, H, N. Further elution provided *cis*-**12m** (0.9 g, 35%): NMR ($CDCl_3$) δ 1.37 (d, 6H, *J* = 5 Hz), 2.97 (septet, 1H, *J* = 5 Hz), 3.58 (s, 3H), 5.96 (d, 1H, *J* = 9 Hz), 6.78 (d, 1H, *J* = 9 Hz), 6.90 (t, 2H, *J* = 9 Hz), 7.05 (t, 2H, *J* = 9 Hz), 7.23 (dd, 2H, *J* = 9 and 6 Hz), 7.43 (dd, 2H, *J* = 9 and 6 Hz).

(*E*)-3-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-2-propenol (13m). To a solution of *trans*-**12m** (1.15 g, 3 mmol) in dry dichloromethane (30 mL) at −78 °C under nitrogen was added DIBAL-*H* (1 M solution in dichloromethane, 6.62 mL). The mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature, quenched with saturated aqueous ammonium chloride, and extracted with dichloromethane. The extracts were combined, dried, and evaporated to give a white solid which was purified by flash column chromatography, eluting with ethyl acetate–cyclohexane (2:3) to give **13m** (0.866 g, 81%) as an off white crystalline solid: IR ($CHBr_3$) 3592, 1661, 1591 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (d, 6H, *J* = 7 Hz), 1.63 (t, 1H, *J* = 5 Hz), 3.14 (septet, 1H, *J* = 7 Hz), 4.16 and 4.17 (2t, 2H, *J* = 5 Hz), 5.51 (dt, 1H, *J* = 15 and 5 Hz), 6.60 (dt, 1H, *J* = 15 and 2 Hz), 6.89 (t, 2H, *J* = 9 Hz), 7.09 (t, 2H, *J* = 9 Hz), 7.25 (dd, 2H, *J* = 9 and 6 Hz), 7.38 (dd, 2H, *J* = 9 and 6 Hz). Anal. ($C_{21}H_{20}F_2N_2O$) C, H, N.

(*E*)-3-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-2-propenal (15m). Manganese(IV) oxide (2.101 g, 7 × w/w) was added to a stirred solution of **13m** (0.301 g, 0.85 mmol) in dichloromethane (30 mL). After 1 h, the reaction mixture was filtered, and the residual manganese(IV) oxide was washed sequentially with ethyl acetate–cyclohexane (1:1) and ethyl acetate. The filtrate was evaporated to give **15m** (0.225 g, 75%) as a white solid: IR ($CHBr_3$) 1680, 1637, 1514, 1232 cm^{-1}; UV λ_{max} 260.9 (ε 20 051) nm in ethanol; NMR ($CDCl_3$) δ 1.49 (d, 6H, *J* = 7 Hz), 3.25 (septet, 1H, *J* = 7 Hz), 5.63 (dd, 1H, *J* = 15 and 7 Hz), 6.92 (t, 2H, *J* = 9 Hz), 7.21 (t, 2H, *J* = 9 Hz), 7.33 (dd, 2H, *J* = 9 and 6 Hz), 7.41 (dd, 2H, *J* = 9 and 6 Hz), 7.51 (d, 1H, *J* = 15 Hz), 9.41 (d, 1H, *J* = 7 Hz). Anal. ($C_{21}H_{18}F_2N_2O$) C, H, N.

Method B. (*E*) 3-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-2-propenal (15m). To a solution of **8m** (492 mg, 1.65 mmol) in dry THF (35 mL) under nitrogen was added propiolaldehyde (0.97 mL), and the reaction mixture was heated to reflux. Further quantities of propiolaldehyde were added in portions (3 × 1.1 g) during successive 2-h periods. The reaction mixture was concentrated, and the deep-red residue was purified by flash column chromatography, eluting with ethyl acetate–cyclohexane (1:4) to give an off-white solid of **15m** (398 mg) as a 1:1 mixture of geometric isomers by ^{1}H-NMR. This isomeric mixture was dissolved in carbon tetrachloride (150 mL) and heated at reflux with iodine (0.1 g) for 18 h using a 200-W tungsten lamp. After this period, activated charcoal (6 g) was added, and heating was continued for a further 1 h. The mixture was filtered, and the resulting pale yellow solution was evaporated to yield **15m** (384 mg, 66%) as a dull-white solid whose spectroscopic properties were in accord with those described above.

Method C. (*E*)-3-[4,5-Bis(4-fluorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-1-yl]-2-propenenitrile (14e). Triethylamine (5.2 mL, 37.31 mmol) was added to a mixture of 4,5-bis(4-fluorophenyl)-2-(trifluoromethyl)-1*H*-imidazole[10] **8e** (3.045 g, 9.4 mmol), 2,3-dibromopropionitrile (5.33 g, 25 mmol), and anhydrous potassium carbonate (3.1 g, 22.4 mmol) in DMF (19 mL) at room temperature under nitrogen. The resulting solution was stirred for 4 days at room temperature. The reaction was quenched with brine, extracted with dichloromethane (5×) and dried. Removal of the solvent gave a brown liquid which was purified by flash column chromatography eluting with ethyl acetate–cyclohexane (1:9) to give **14e** (1.45 g, 41%) as a white solid: IR ($CHBr_3$) 2229 cm^{-1}; NMR ($CDCl_3$) δ 5.11 (d, 1H, *J* = 15 Hz), 6.96 (t, 2H, *J* = 9 Hz), 7.2–7.5 (m, 7H). Anal. ($C_{29}H_{10}F_8N_3$) C, H, N.

(*E*)-3-[4,5-Bis(4-fluorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-1-yl]-2-propenal (15e). DIBAL-*H* (1 M in dichloromethane, 2.2 mL) was added to a solution of **14e** (484 mg, 1.29 mmol) in dry THF (15 mL) at −78 °C under nitrogen. The resulting mixture was stirred at −78 °C for 1.5 h. The reaction was quenched with saturated aqueous ammonium chloride, extracted with dichloromethane (4×), and dried. Rotary evaporation gave a brown gum (0.53 g) which was purified by flash column chromatography, eluting with ethyl acetate–cyclohexane (1:9) to give **15e** (263 mg, 54%) as a yellow solid: IR (Nujol) 1692, 1226 cm^{-1}; NMR ($CDCl_3$) δ 5.77 (dd, 1H, *J* = 14.7 and 7.4 Hz), 6.95 (t, 2H, *J* = 8.7 Hz), 7.2–7.3 and 7.31–7.46 (2 m, 6H), 7.55 (d, 1H, *J* = 14.7 Hz), 9.47 (d, 1H, *J* = 7.4 Hz).

(±)-(*E*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-5-hydroxy-3-oxo-6-heptenoic Acid, Methyl Ester (16m). To a slurry of sodium hydride [60% dispersion in oil, 0.10 g, 2.5 mmol, washed with dry THF (3 × 3 mL)] in THF (2 mL) at −3 °C under nitrogen was added methyl acetoacetate (0.028 mL, 0.26 mmol). After 5 min, *n*-butyllithium (1.4 M in hexanes, 0.26 mL) was added, and the resultant solution was stirred at −3 °C for 10 min. **15m** (0.10 g, 0.28 mmol) in THF (9

mL) was cannulated into the methyl acetoacetate dianion solution at −3 °C. After 0.5 h at −3 °C the cooling bath was removed and after a further 10 min the mixture was recooled to 0 °C and then quenched with saturated aqueous ammonium chloride (50 mL). The solution was extracted with dichloromethane (50 mL × 4), and the extracts were combined, dried, and evaporated to give a dark orange oil. This material was purified by flash column chromatography eluting with ethyl acetate–cyclohexane (2:3, 1:1) to give **16m** (0.054 g, 41%) as an orange solid: R_f 0.18 (SiO_2/ethyl acetate–cyclohexane, 2:3); IR ($CHBr_3$) 3560, 1742, 1713 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (d, 6H, J = 7 Hz), 2.62 (d, 2H, J = 5 Hz), 2.93 (br s, 1H), 3.12 (septet, 1H, J = 7 Hz), 3.46 (s, 2H), 3.77 (s, 3H), 4.63 (m, 1H), 5.27 (dd, 1H, J = 15 and 5 Hz), 6.72 (dd, 1H, J = 15 and 2 Hz), 6.91 (t, 2H, J = 8 Hz), 7.11 (t, 2H, J = 8 Hz), 7.24 (dd, 2H, J = 8 and 5 Hz), 7.42 (dd, 2H, J = 8 and 5 Hz). Anal. ($C_{26}H_{26}F_2N_2O_4$) C, H, N.

(±)-*erythro*-(*E*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (17m). To a solution of triethylborane (1 M in THF, 0.36 mL) in THF (1.7 mL) at room temperature under nitrogen was added dried methanol (0.35 mL), and the mixture was stirred for 1 h. The solution was then cooled to −78 °C, and **16m** (52 mg, 0.11 mmol) in THF (4 mL) was added. The mixture was stirred for 1 h, after which time sodium borohydride (5 mg, 0.13 mmol) was added. After 6 h of stirring at −78 °C, the reaction mixture was diluted with ethyl acetate (10 mL), and the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) at −78 °C. The mixture was allowed to warm to room temperature overnight, extracted with ethyl acetate (5 × 20 mL), and dried. Rotary evaporation gave a residue which was azeotroped with methanol (4 × 30 mL) to give the crude product as an orange film. Purification by flash column chromatography eluting with ethyl acetate–cyclohexane (2:1) gave **17m** (46 mg, 88%) as a clear colorless film: R_f 0.20 (SiO_2/ethyl acetate–cyclohexane, 2:1); NMR ($CDCl_3$) δ 1.3–1.8 (m, 2H), 1.4 (d, 6H, J = 7 Hz), 3.8–4.0 (br s, 2H), 4.10–4.21 (m, 1H), 4.37–4.46 (m, 1H), 5.31 (dd, 1H, J = 15 and 5 Hz), 6.66 (dd, 1H, J = 15 and 2 Hz), 6.90 and 7.09 (2 t, 4H, J = 9 Hz for both), 7.03–7.12 and 7.35–7.44 (2 m, 4H). Anal. ($C_{26}H_{28}F_2N_2O_4 \cdot 0.42H_2O$) C, H, N, H_2O.

(±)-erythro-(*E*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Sodium Salt (5m). To a stirred solution of **17m** (44 mg, 0.093 mmol) in THF (0.5 mL) under nitrogen was added aqueous sodium hydroxide (0.1M, 0.84 mL). After 0.6 h the solution was rotary evaporated to remove all organic solvent. The residual aqueous solution was diluted with water (10 mL) and extracted with ether (4 × 20 mL). The aqueous phase was filtered, concentrated (ca. 5 mL), and subjected to freeze-drying overnight to give **5m** as a beige solid (37 mg): IR (Nujol) 3345, 1570, 1518, 1461, 1224 cm^{-1}; NMR (d_6-DMSO) δ 1.00–1.50 (m, 2H), 1.30 (d, 6H, J = 7 Hz), 1.70–1.82 and 1.94–2.03 (2 m, 2H), 3.16 (septet, 1H, J = 7 Hz), 3.47–3.6 (m, 1H), 4.13–4.23 (m, 1H), 5.15–5.28 (br s, 1H), 5.48 (dd, 1H, J = 15 and 5 Hz), 6.55 (d, 1H, J = 15 Hz), 7.06 (t, 2H, J = 9 Hz), 7.22–7.43 (m, 6H). Adjustment of the aqueous solution of **5m** to pH 4 with 2 M hydrochloric acid followed by extraction of the ammonium sulfate saturated aqueous solution gave the free acid: Anal. ($C_{25}H_{28}F_2N_2O_4 \cdot 0.3H_2O$) C, H, N, F.

(*E*,3*S*)-5-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3-hydroxy-4-pentenoic Acid, (*S*)-1,1,2-Triphenylethyl Ester (24). A solution of dry dicyclohexylamine (2.49 mL, 12.5 mmol) in dry THF (30 mL) under nitrogen at 3 °C was treated dropwise with a solution of *n*-butyllithium (1.55 M in hexanes, 8.06 mL). After 25 min the solution was cannulated dropwise into a stirred suspension of (*S*)-2-acetoxy-1,1,2-triphenylethanol[18] (1.828 g, 5.5 mmol) in dry THF (60 mL) under nitrogen at −40 °C, plus washings (10 mL). When the addition was complete the mixture was allowed to warm to 3 °C. After 20 min the solution was cooled to −40 °C and treated with a solution of **15m** (1.762 g, 5 mmol) in dry THF (40 mL). After 4 h the reaction mixture was treated with saturated aqueous ammonium chloride solution (20 mL) and allowed to warm to room temperature. Water (200 mL) was then added, and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried and evaporated and purified by flash column chromatography with ethyl acetate–cyclohexane (7:3) to give **24** (3.234 g, 94%), as a light brown foam: IR ($CHBr_3$) 3638, 2971, 1729, 1517, 1224, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.36 and 1.38 (2 d, 6H, J = 7 Hz for both), 2.30 (d, 2H, J = 6 Hz), 2.68 (d, 1H, J = 4.5 Hz), 2.78 (s, 1H), 3.05 (septet, 1H, J = 7 Hz), 4.32–4.45 (m, 1H), 5.38 (dd, 1H, J = 14 and 5 Hz), 6.58 (dd, 1H, J = 14 and 2 Hz), 6.72 (s, 1H), 6.89 (t, 2H, J = 9 Hz), 7.0–7.2, 7.23–7.43, and 7.5–7.6 (3 m, 21H). *SS*:*SR* = 93:7 by ^{1}H-NMR. Anal. ($C_{43}H_{38}F_2N_2O_4 \cdot 0.7H_2O$) C, H, N.

(*E*,3*S*)-5-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3-hydroxy-4-pentenoic Acid, Methyl Ester (25). A stirred suspension of **24** (3.11 g, 4.54 mmol) in methanol (30 mL) was treated with a solution of sodium (110 mg, 4.78 mmol) in methanol (20 mL) plus methanol washings (2 × 5 mL). The resulting orange solution was stirred at room temperature for 2.5 h, and then the reaction mixture was concentrated. This was dissolved in dichloromethane (150 mL), and then the solution was washed with water (50 mL) and brine (2 × 50 mL). The combined washings were extracted with dichloromethane (50 mL), and the combined organic phases were dried and evaporated to a pale buff solid (3.13 g). This was purified by column chromatography eluting with ethyl acetate–cyclohexane, 1:1, to give **25** (1.588 g, 82%) as a white crystalline solid: $[\alpha]^{20}_D$ = +10.3° (0.3% in $CHCl_3$); IR (Nujol) 3176, 1739, 1512, 835 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (d, 6H, J = 7 Hz), 2.3–2.5 (m, 2H), 3.11 (d, 1H, J = 5 Hz), 3.13 (septet, 1H, J = 7 Hz), 3.71 (s, 3H), 4.50–4.61 (m, 1H), 5.30 (dd, 1H, J = 14.5 and 5.5 Hz), 6.71 (dd, 1H, J = 14.5 and 2 Hz), 6.90 and 7.09 (2 t, 4H, J = 9 Hz for both), 7.23 and 7.39 (dd, 2H, J = 9 and 5.5 Hz for both); MS ($C_{24}H_{26}F_2N_2O_3$) calcd 427.1833, found 427.1824.

(*E*,5*S*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-5-hydroxy-3-oxo-6-heptenoic Acid, 1,1-Dimethyleth-1-yl Ester (26). A solution of dry diisopropylamine (0.77 mL, 5.49 mmol) in dry cyclohexane (15.6 mL) at 3 °C under nitrogen was treated dropwise with *n*-butyllithium solution (1.55 M in hexanes, 3.54 mL). After 15 min *tert*-butyl acetate (0.74 mL, 5.49 mmol) was added dropwise. After 30 min the mixture was cannulated into a solution of **25** (334 mg, 0.78 mmol) in dry THF (7.8 mL) at 3 °C under nitrogen over 15 min. After 1 h the mixture was quenched with saturated aqueous ammonium chloride solution (3.5 mL) and then diluted with water. The mixture was then extracted with ethyl acetate (3 × 20 mL). The combined extracts were dried and evaporated to a gummy solid (518 mg) which was treated with ether (4 mL) and then cyclohexane (4 mL) and cooled in an ice bath. The solid was collected, washed, and dried to give **26** (239 mg, 60%) as a white powder: $[\alpha]^{20}_D$ = −7.7° (1.04% in $CHCl_3$); IR ($CHBr_3$) 3660, 1728, 1707, 1517, 1224, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.41 (d, 6H, J = 7.5 Hz), 1.46 (s, 9H), 2.59 (d, 2H, J = 5.5 Hz), 3.02 (br s, 1H), 3.14 (septet, 1H, J = 7.5 Hz), 3.35 (s, 2H), 4.57–4.68 (m, 1H), 5.39 (dd, 1H, J = 14 and 7 Hz), 6.70 (d, 1H, J = 14 Hz), 6.90 and 7.10 (2 t, 4H, J = 9 Hz for both), 7.24 and 7.38 (2 dd, 4H, J = 8 and 5.5 Hz for both). About 8% of enol form was present: δ includes 2.29 (d, J = 5.5 Hz), 4.51 (m), 4.89 (s), 5.38 (dd, J = 14 and 7 Hz), 6.64 (d, J = 14 Hz). Anal. ($C_{29}H_{32}F_2N_2O_4$) C, H, N. Chiral HPLC, performed on an AGP column (4-mm diameter × 100-mm length) at ambient temperature using 20 mM NaH_2PO_4 pH 4.0 buffer containing 3% propan-2-ol as eluant at 0.3 mL/min, detected none of the other enantiomer possessing the longer retention time at 230-nm wavelength (t_R = 11.9 and 14.8 min for the corresponding racemate). A second crop of **26** (56 mg) was also obtained.

(*E*,3*R*,5*S*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, 1,1-Dimethyleth-1-yl Ester (27). A solution of dry THF (16 mL) and dry methanol (4 mL) under nitrogen at room temperature was treated with a solution of triethylborane (1.0 M in THF, 2.32 mL). After 1 h the mixture was cooled to −78 °C and treated with a solution of **26** (1.075 g, 2.1 mmol) in THF (15 mL) plus washings (5 mL). After a further 1 h at -75 °C the mixture was treated with sodium borohydride (88 mg, 2.3 mmol). After 2.5 h the mixture was quenched with saturated aqueous ammonium chloride solution (2 mL) and allowed to warm to room temperature. The mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3 × 70 mL). The combined extracts were dried and evaporated, and the residue was azeotroped with methanol (3 × 30 mL). This gave a pale yellow solid (1.076 g) which was crystallized from ether–cyclohexane to give **27** (739

mg, 68%) as white fluffy crystals: $[\alpha]^{20}_D = -70°$ (0.7% in $CHCl_3$); NMR ($CDCl_3$) δ 1.31–1.57 (m, 2H), 1.43 (d, 6H, J = 7.5 Hz), 1.50 (s, 9H), 2.38 (d, 2H, J = 7 Hz), 3.17 (septet, 1H, J = 7.5 Hz), 3.78 (s, 1H), 3.81 (s, 1H), 4.09–4.17 (m, 1H), 4.40–4.46 (m, 1H), 5.31 (dd, 1H, J = 14 and 5 Hz), 6.69 (d, 1H, J = 14 Hz), 6.91 (t, 2H, J = 9 Hz), 7.09 (t, 2H, J = 9 Hz), 7.27 (dd, 2H, J = 9 and 5 Hz), 7.50 (dd, 2H, J = 9 and 5 Hz). Anal. ($C_{29}H_{34}F_2N_2O_4$) C, H, N. HPLC showed >99:1; *syn:anti*.

(*E*,3*R*,5*S*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic acid (28). A solution of **27** (726 mg, 1.4 mmol) in redistilled THF (40 mL) was treated with 0.1 M aqueous sodium hydroxide solution (14.5 mL). After 30 min the mixture was concentrated to ca. 10 mL and then diluted with water (50 mL). The mixture was acidified to pH 2 with 2 M hydrochloric acid and brought back to pH 4 with aqueous sodium hydrogen carbonate solution, ammonium sulfate was added, and then the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried and concentrated to ca. 4 mL when a solid crystallized. The crystals were collected and dried to give **28** (500 mg, 77%): mp 172–3 °C; $[\alpha]^{20}_D = +15.7°$ (1.02% in DMSO); IR (Nujol) 3402, 1692, 1519, 1223, 845 cm^{-1}; NMR (d_6-DMSO) δ 1.20–1.40 and 1.45-1.59 (2 m, 2H), 1.28 (d, 6H, J =7 Hz), 2.19 (dd, 1H, J = 15 and 8 Hz), 2.29 (dd, 1H, J = 15 and 5 Hz), 3.18 (septet, 1H, J = 7 Hz), 3.67–3.83 (m, 1H), 4.10–4.24 (m, 1H), 4.60–4.80 (br s, 1H), 5.00 (d, 1H, J = 4.5 Hz), 5.46 (dd, 1H, J = 14 and 6.5 Hz), 6.59 (d, 1H, J = 14 Hz), 7.05 (t, 2H, J = 8.5 Hz), 7.21–7.43 (m, 6H). Anal. ($C_{25}H_{26}F_2N_2O_4$) C, H, N, F. *RS:SR* = 99.5:0.5 by HPLC.

(*E*,3*S*,5*R*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, 1,1-Dimethyleth-1-yl Ester (33) was prepared by procedures similar to that described for the preparation of **27** using (*R*)-2-acetoxy-1,1,2-triphenylethanol: mp 164 °C; $[\alpha]^{20}_D = -30°$ (1% in MeOH); NMR was identical to that described for compound **27**. Anal. ($C_{29}H_{34}F_2N_2O_4 \cdot 0.2H_2O$) C, H, N.

(*E*,3*S*,5*R*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid (31). Compound **31** was prepared from compound **33** by a procedure similar to that described for the preparation of **28**: mp 169 °C; $[\alpha]^{20}_D = -15°$ (1% in DMSO); NMR was identical to that described for compound **28**. Anal. ($C_{25}H_{26}F_2N_2O_4$) C, H, N. HPLC showed 0.6% *anti* isomer. Chiral HPLC showed the absence of **28**.

(*E*,3*R*,5*R*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, 1,1-Dimethyleth-1-yl Ester (34). Tetramethylammonium borohydride (4.3 g, 48 mmol) was added over 10 min to acetic acid (110 mL) while the temperature was kept at ca. 20 °C with an ice–water bath. After the evolution of hydrogen, the solution was stirred for 10 min. (*E*,5*R*) 7-[4,5-Bis(4-fluorophenyl-2-(1-methylethyl)-1*H*-imidazol-1-yl]-5-hydroxy-3-oxo-6-heptenoic acid, 1,1- dimethyleth-1-yl ester (prepared by a procedure similar to that described for **26**) (6 g, 11.7 mmol) was added over 3 min and stirred for 1 h at 15–20 °C. The reaction was quenched carefully with water (45 mL), and the mixture was stirred with ethyl acetate (215 mL) and saturated brine (25 mL) for 5 min. The organic solution was separated and washed with aqueous sodium bicarbonate solution (7 × 55 mL) until the aqueous extract remained alkaline and brine (40 mL). Removal of solvent gave a solid which was dissolved in ethyl acetate (15 mL) at 60 °C. Petroleum ether (60–80 °C, 90 mL) was added over 5 min. The solution was allowed to cool to 5 °C over 2 h. The crystallized solid was collected by filtration and washed with petroleum ether–ethyl acetate (6:1) (2 × 10 mL) and petroleum ether (10 mL) to give **34** (5.0 g, 83%): IR (Nujol) 3468, 3391, 1718, 1697, 1512, 1213, 1147, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.36 (d, 6H, J = 7 Hz), 1.42 (s, 9H), 1.52–1.71 (m, 2H), 2.17–2.40 (m, 2H), 3.10 (septet, 1H, J = 7 Hz), 3.29 (br s, 1H), 3.61 (br s, 1H), 3.89–4.07 (m, 1H), 4.42 (br s, 1H), 5.34 (dd, 1H, J = 14.5 and 5 Hz), 6.64 (dd, 1H, J = 14.5 and 1.5 Hz), 6.81 (t, 2H, J = 9 Hz), 7.03 (t, 2H, J = 9 Hz), 7.20 (dd, 2H, J = 9 and 5.5 Hz), 7.33 (dd, 2H, J = 9 and 5.5 Hz). Anal. ($C_{29}H_{34}F_2N_2O_4$) C, H, N. HPLC showed 3.6% of the *syn* isomer.

(*E*,3*R*,5*R*)-7-[4,7-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid (32). Compound **32** was prepared from compound **34** by a procedure similar to that described for the preparation of **28**: mp 122 °C; $[\alpha]^{20}_D = +11°$ (1% in DMSO); IR (Nujol) 3390, 1675, 1517, 1219, 846 cm^{-1}; NMR (d_6-DMSO) δ 1.11–1.44 (m, 2H), 1.30 (d, 6H, J = 7 Hz), 2.12–2.38 (m, 2H), 3.16 (septet, 1H, J = 7 Hz), 3.91–4.08 (m, 1H), 4.12–4.30 (m, 1H), 4.90 (br s, H), 5.51 (dd, 1H, J = 14 and 6 Hz), 6.58 (d, 1H, J = 14 Hz), 7.03 (t, 2H, J = 9 Hz), 7.19–7.48 (m, 6H). Anal. ($C_{25}H_{28}F_2N_2O_4 \cdot 0.15H_2O$) C, H, N. Chiral HPLC showed the absence of **30**.

(*E*,3*S*,5*S*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, 1,1-Dimethyleth-1-yl Ester (29). Compound **29** was prepared from **26** by a procedure similar to that described for the preparation of **34** except that sodium borohydride was used instead of tetramethylammonium borohydride: mp 135 °C; IR and NMR were identical to that described for compound **34**. Anal. ($C_{29}H_{34}F_2N_2O_4 \cdot 0.2H_2O$) C, H, N. Chiral HPLC showed 94.3% purity.

(*E*,3*S*,5*S*)-7-[4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-1-yl]-3,5-dihydroxy-6-heptenoic Acid (30). Compound **30** was prepared from compound **29** by a procedure similar to that described for the preparation of **28**: mp 122 °C; $[\alpha]^{20}_D = -8°$ (0.5% in DMSO); IR and NMR were identical to that described for compound **32**. Anal. ($C_{25}H_{28}F_2N_2O_4 \cdot 0.5H_2O$) C, H, N. Chiral HPLC showed 99% purity.

(±)-erythro-(*E*)-3,5-Dihydroxy-7-[5-(4-fluorophenyl)-2-(1-methylethyl)-4-[3-(methylsulfonyl)phenyl]-1*H*-imidazol-1-yl]-6-heptenoic Acid, Methyl Ester (17ak). To a mixture of **18** and the corresponding N3-alkylated regioisomer (40 mg, 0.08 mmol), prepared by a procedure similar to that described for the preparation of **17m**, in methanol (7 mL) was added selenium(IV) oxide (9 mg, 0.08 mmol) and 30% hydrogen peroxide solution (0.05 mL). The mixture was stirred at room temperature, and after 2 and 4 h further additions of 30% hydrogen peroxide solution (0.1 mL) were made. The mixture was stirred at room temperature for 18 h and was then evaporated. The residue was purified by column chromatography, eluting with ethyl acetate–methanol (19:1) to give a pale yellow gum (45 mg).

Preparative HPLC on a Zorbax-NH_2 column eluting with 80% (cyclohexane–dichloromethane–methanol (75:20:5)): 20% (cyclohexane–dichloromethane (80:20)) gave **17ak** (16 mg, 38%): R_f 0.23 (SiO_2/ethyl acetate); NMR ($CDCl_3$) δ 1.3–1.6 (m, 2H), 1.41 (d, 6H, J = 7 Hz), 2.46 (d, 2H, J = 7 Hz), 2.97 (s, 3H), 3.15 (septet, 1H, J = 7 Hz), 3.67 (br s, 1H), 3.71 (br s, 1H), 3.74 (s, 3H), 4.09–4.24 (m, 1H), 4.39–4.50 (m, 1H), 5.35 (dd, 1H, J = 14 and 5 Hz), 6.69 (dd, 1H, J = 14 and 1 Hz), 7.12 (t, 2H, J = 9 Hz), 7.26 (dd, 2H, J = 9 and 5.5 Hz), 7.36 (t, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz), 7.71 (d, 1H, J = 7.5 Hz), 8.10 (s, 1H). Further elution gave the regioisomer of **17ak**, **(±)-*erythro*-(*E*)-3,5-dihydroxy-7-[4-(4-fluorophenyl)-2-(1-methylethyl)-5-[3-(methylsulfonyl)phenyl]-1*H*-imidazol-1-yl]-6-heptenoic acid, methyl ester** (9.4 mg, 22%): R_f 0.29 (SiO_2/ethyl acetate); NMR ($CDCl_3$) δ 1.47–1.7 (m, 2H), 1.41 (d, 6H, J = 6.5 Hz), 2.49 (d, 2H, J = 6 Hz), 3.07 (s, 3H), 3.15 (septet, 1H, J = 6.5 Hz), 3.71 (s, 3H), 3.76 (br s, 1H), 3.87 (br s, 1H), 4.15–4.30 (m, 1H), 4.43–4.54 (m, 1H), 5.41 (dd, 1H, J = 14 and 6 Hz), 6.68 (d, 1H, J = 14 Hz), 6.93 (t, 2H, J = 9 Hz), 7.40 (dd, 2H, J = 9 and 5 Hz), 7.51–7.59 (m, 2H), 7.82–7.92 (m, 2H).

4(5)-(3-Aminophenyl)-5(4)-(4-fluorophenyl)-2-(1-methylethyl)-1-[2-[(trimethylsilyl)ethoxy]ethyl]-1*H*-imidazole (20). A solution of **19**[10] (40.35 g, 124 mmol) in dry THF (1320 mL) was treated dropwise with a toluene solution of potassium bis(trimethylsilyl)amide (0.5 M, 297 mL) under nitrogen at −78 °C. When the addition was complete, the mixture was stirred at −78 °C for 0.5 h, and then [2-(trimethylsilyl)ethoxy]methyl chloride (24.6 mL, 139 mmol) was added. The mixture was allowed to stir and warm to room temperature over 2.25 h. Brine was added to quench the reaction, and the mixture was extracted three times with ethyl acetate. The combined extracts were dried and evaporated to give a brown liquid. Purification by filtration chromatography eluting with ethyl acetate–cyclohexane (1:4) gave an impure sample of the SEM protected imidazole (64.1 g, quantitative) in a (2:5) ratio as a brown liquid: R_f 0.51 (SiO_2/ethyl acetate–cyclohexane (1:1)); NMR ($CDCl_3$) δ 0.00 and 0.03 (2 s, 9H), 0.88 and 0.99 (2 dd, 2H, J = 8.5 and 8 Hz), 1.49 (d, 6H, J = 7.5 Hz), 3.21 (septet, 1H, J = 7.5 Hz), 3.39 and 3.48 (2 dd, 2H, J = 8.5 and 8 Hz), 5.06 (s, 2H), 6.93 and 7.20 (2 t, 2H, J = 8.5 Hz), 7.3–7.8 (m, 4H), 7.99 and 8.28 (2 dm, 1H, J = 8.7 Hz).

THF (130 mL) was added dropwise to a stirred mixture of sodium borohydride (17.16 g, 0.45 mol) and sulfur (41.40 g, 1.29 ml) at 0 °C. The resulting slurry was stirred for 0.5 h at room

temperature, and then a solution of the SEM protected imidazole (64.1 g, 0.141 mol) in THF (800 mL) was added. The mixture was stirred at room temperature for 18 h, heated at reflux for 2.5 h, and then allowed to cool. The solution was cooled to 0 °C, and 5% aqueous sodium hydroxide solution (2000 mL) and ethyl acetate (1000 mL) were added simultaneously over 1 h. The organic phase was separated, and the aqueous phase was extracted into 2 M hydrochloric acid (3 × 750 mL). The acidic aqueous layers were combined, washed with ethyl acetate (1000 mL), and then basified using 3 M aqueous sodium hydroxide solution. The product was extracted into ethyl acetate (3 × 1000 mL), and the extracts were washed with water (1000 mL), dried, and evaporated to give **20** (47.12 g, 79%) in a 2:3 ratio as a brown gum: R_f 0.51 and 0.21 (SiO_2/ethyl acetate–cyclohexane (1:1)); NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.85 and 0.86 (2 t, 2H, J = 8 Hz), 1.46 and 1.47 (2 d, 6H, J = 7 Hz), 3.20 and 3.21 (2 septet, 1H, J = 7 Hz), 3.37 (t, 2H, J = 8 Hz), 5.05 and 5.10 (2 s, 2H), 6.45-7.00 (m, 4H), 7.15 and 7.25 (2 t, 2H, J = 9 Hz), 7.38 and 7.51 (2 dd, 2H, J = 9 and 5.5 Hz).

***N*-[3-(4(5)-(4-Fluorophenyl)-2-(1-methylethyl)-1-[2-[(trimethylsilyl)ethoxy]ethyl]-1*H*-imidazol-5(4)-yl)phenyl]carbamic Acid, 1,1-Dimethyleth-1-yl Ester (21).** Water (470 mL) was added to a stirred solution of **20** (47.2 g, 0.111 mol) in 1,4-dioxan (700 mL). To the resultant solution was added di-*tert*-butyl dicarbonate (28.99 g, 0.133 mol) followed by anhydrous sodium carbonate (23.38 g, 0.22 mol). After 21 h at room temperature, the reaction mixture was separated into two portions and each partitioned between ethyl acetate (1000 mL) and water (1000 mL). The organic phases were separated and the aqueous phases extracted with ethyl acetate (2 × 750 mL). The combined organic phases were dried and evaporated to give a brown/orange liquid which was purified by column chromatography, eluting with ethyl acetate–cyclohexane ((1:19), (1:9), (3:17), and (1:4)) to give **21** (49.03 g, 84%) in a (3:7) ratio as a yellow solid: R_f 0.35 and 0.21 (SiO_2/ethyl acetate–cyclohexane (1:4)); NMR ($CDCl_3$) δ −0.02 and 0.04 (2 s, 9H), 0.84 and 0.86 (2 t, 2H, J = 8 Hz), 1.46 (d, 6H, J = 7 Hz), 1.54 and 1.55 (2 s, 9H), 3.20 and 3.21 (2 septet, 1H, J = 7 Hz), 3.34 and 3.37 (2 t, 2H, J = 8 Hz), 5.05 and 5.10 (2 s, 2H), 6.40 and 6.53 (2 br s, 1H), 6.85–7.20 (m, 4H), 7.30-7.55 (m, 4H).

***N*-[3-(4(5)-(4-Fluorophenyl)-2-(1-methylethyl)-1*H*-imidazol-5(4)-yl)phenyl]-*N*-methylcarbamic Acid, 1,1-Dimethyleth-1-yl Ester (22).** Sodium hydride (5.59 g of 60% dispersion in oil, 0.14 mol) was added over 5 min to a stirred solution of **21** (48.95 g, 93.2 mmol) in dry DMF (460 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and at room temperature for 1 h. Methyl iodide (19.87 g, 0.14 mol) was then added, and the solution was stirred at room temperature for 3 h. The mixture was then quenched with water and partitioned between water (1700 mL) and ethyl acetate (1700 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 850 mL). The combined organic solutions were dried and evaporated, and the residue was purified by suction flash chromatography eluting with ethyl acetate–cyclohexane ((0:1), (1:19), (3:17), (1:4)) to give a brown/orange gum (53.36 g). This crude product was heated with tetra-*n*-butylammonium fluoride (900 mL of a 1.0 M solution in THF, 0.9 mol) at reflux for 5 h then allowed to cool overnight. The mixture was concentrated to $^1/_3$ volume, diluted with ethyl acetate (1700 mL), and washed with water (2 × 2000 mL). The organic phase was then dried and evaporated, and the residue was purified by column chromatography, eluting with ethyl acetate–cyclohexane ((3:7), (1:1)) to give **22** (34.91 g, 88%) as a mixture of tautomers as a yellow foam: R_f 0.30 (SiO_2/ethyl acetate–cyclohexane (1:1)); NMR ($CDCl_3$) δ 1.34 (d, 6H, J = 7 Hz), 1.45 (s, 9H), 3.07 (septet, 1H, J = 7 Hz), 3.18 (s, 3H), 6.96 (t, 2H, J = 8.5 Hz), 7.06–7.50 (m, 6H), 9.66 (v br s, 1H).

(±)-*erythro*-(*E*)-3,5-Dihydroxy-7-[5-(4-fluorophenyl)-4-[3-(methylamino)phenyl]-2-(1-methylethyl)-1*H*-imidazol-1-yl]-6-heptenoic Acid, Methyl Ester (17al). Trifluoroacetic acid (25 mL) was added to a stirred solution of **23** [prepared by a procedure similar to that described for **17m**] (1.046 g, 1.8 mmol) in anisole (9 mL) at 0 °C. After 0.5 h, ethyl acetate (150 mL) was added, and the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution and solid sodium hydrogen carbonate until the aqueous phase was pH 8. The aqueous phase was extracted with ethyl acetate (2 × 300 mL), and the combined organic phases were dried, evaporated, and purified by column chromatography eluting with ethyl acetate–cyclohexane ((1:1), (17:3), (1:0)) and then ethyl acetate–methanol (9:1) to give **17al** (0.777 g, 90%) as a pale yellow foam: R_f 0.12 (SiO_2/ethyl acetate–cyclohexane (4:1)); NMR ($CDCl_3$) δ 1.40 (d, 6H, J = 7 Hz), 1.30–1.60 (m, 2H), 2.44 (d, 2H, J = 6 Hz), 2.70 (s, 3H), 3.13 (septet, 1H, J = 7 Hz), 3.32 (br s, 3H), 3.72 (s, 3H), 4.1–4.2 (m, 1H), 4.35–4.45 (m, 1H), 5.30 (dd, 1H, J = 15 and 6 Hz), 6.42 (dd, 1H, J = 15 and 2 Hz), 6.60–6.80 (m, 3H), 6.95-7.10 (m, 3H), 7.20–7.30 (m, 2H).

X-ray Crystallography of 28. Crystal data: $C_{25}H_{26}N_2O_4F_2$, M = 456.49, orthorhombic, a = 5.688 (1), b = 18.119 (4), c = 23.064 (7) Å, V = 2377 (2) Å^3 (by least-squares refinement on diffractometer angles for 12 automatically centred reflections, λ = 1.54184 Å). Space group $P2_12_12_1$ (No. 19), Z = 4, D_c = 1.28 g cm^{-3}. $F(000)$ = 960, μ(Cu Kα) = 7.8 cm^{-1}; crystallizes from ethyl acetate as colorless needles, data crystal approximately 0.20 × 0.08 × 0.04 mm.

Data collection and processing: three-dimensional, room-temperature (295K) X-ray data collected on a Siemens R3m/V diffractometer with monochromatized Cu-Kα X-radiation; 2θ/ω mode with scan range (ω) 1.14° plus Kα separation and a variable scan speed (1.95–14.65 deg min^{-1}); a total of 3128 reflections measured ($0 < 2\theta < 115°$, min hkl −6 0 0, max hkl 6 19 25); 2937 unique reflections [$R(\sigma)$ = 0.060, Friedel opposites merged]; 883 reflections with $I > 3.0\,\sigma(I)$. No absorption correction was applied. Two control reflections monitored every 98 reflections showed no appreciable decay during 45.8 h of exposure of the crystal to X-rays.

Structure analysis and refinement: direct methods resulted in the location of all the non-hydrogen atoms; full matrix least-squares refinement with anisotropic thermal parameters for all non-hydrogen atoms; hydrogen atoms bonded to carbon were refined in riding mode; H atoms bonded to oxygen were refined freely without constraints; individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0025|F_o|^2]^{-1}$, refinement converged at R = 0.050, R_w = 0.051, goodness-of-fit = 0.91. Refining the Rogers eta parameter[25] [η = 0.7 (6)] gave as expected a poor indication of absolute structure due to the absence in the molecule of a strong anomalous scattering atom. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs.[26]

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Supplementary Material Available: NMR, microanalyses, accurate masses, and X-ray data (13 pages); observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

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