Acknowledgment. We are indebted to E. H. Ferguson and C. S. Sekerke for conducting the enzyme inhibition assays, to Dr. S. Brennan, T. Hurley, and D. Sherwood for HPLC analyses, to Dr. F. A. MacKellar and staff for analytical and spectral determinations, and to P. Carr and D. Sandy for manuscript preparation.

Registry No. 1 (R_1 = Ph), 768-03-6; 1 (R_1 = 4-F-C_6H_4), 51594-59-3; 1 (R_1 = 4-Ph-C_6H_4), 42575-11-1; 1 (R_1 = 4-Cl-C_6H_4), 7448-87-5; 1 (R_1 = 4-CH_3O-C_6H_4), 7448-86-4; 1 (R_1 = 3-F_3C-C_6H_4), 123184-14-5; 1 (R_1 = 3-CH_3O-C_6H_4), 51594-60-6; 1 (R_1 = 2-CH_3O-C_6H_4), 77942-10-0; 1 (R_1 = 2-naphthyl), 4452-06-6; 1 (R_1 = 1-naphthyl), 22422-69-1; 1 (R_1 = bicyclo[2.2.1]-hept-5-en-2-yl), 100234-78-4; 1 (R_1 = bicyclo[2.2.2]-oct-5-en-2-yl), 123184-15-6; 1 (R_1 = cyclohexyl), 2177-34-6; 1 (R_1 = Ph_2CH), 93021-71-7; 1 (R_1 = $CH(C_2H_5)_2$), 123184-16-7; 1 (R_1 = 2-F-C_6H_4), 89638-21-1; 1 (R_1 = 2,4-F_2-C_6H_3), 123184-17-8; 1 (R_1 = $CH(CH_3)_2$), 1606-47-9; 2 (R_2 = CH_3), 75-07-0; 2 (R_2 = $CH(CH_3)_2$), 78-84-2; 2 (R_2 = $CH(C_2H_5)_2$), 97-96-1; 2 (R_2 = cyclopropyl), 1489-69-6; 2 (R_2 = cyclobutyl), 2987-17-9; 2 (R_2 = cyclohexyl), 2043-61-0; 2 (R_2 = $C(CH_3)_3$), 630-19-3; 2 (R_2 = 4-F-C_6H_4), 459-57-4; 2 (R_2 = C_2H_5), 123-38-6; **3a**, 583-05-1; **3b**, 123183-95-9; **3c**, 63472-37-7; **3d**, 53842-12-9; **3e**, 2108-54-5; **3f**, 123183-96-0; **3g**, 123183-97-1; **3h**, 104562-48-3; **3i**, 123183-98-2; **3j**, 123263-79-6; **3k**, 70353-45-6; **3l**, 123183-99-3; **3m**, 61771-79-7; **3n**, 123184-00-9; **3o**, 123184-01-0; **3p**, 104568-68-5; **3q**, 123184-02-1; **3r**, 123184-03-2; **3s**, 123184-04-3; **3t**, 123184-05-4; **3u**, 123184-06-5; **3v**, 123184-07-6; **3w**, 123184-08-7; **3x**, 123184-09-8; **3y**, 123184-10-1; **3z**, 123184-11-2; **3aa**, 123184-12-3; **3bb**, 123184-13-4; **5a**, 123184-20-3; **5b**, 123184-21-4; **5c**, 123184-22-5; **5d**, 123184-23-6; **5e**, 123184-89-4; **5f**, 123184-24-7; **5g**, 123184-25-8; **5h**, 123184-26-9; **5i**, 123184-27-0; **5j**, 123184-28-1; **5k**, 123184-29-2; **5l**, 123184-30-5; **5m**, 123184-31-6; **5n**, 123184-32-7; **5o**, 123184-33-8; **5p**, 123184-34-9; **5q**, 123184-35-0; **5r**, 123184-36-1; **5s**, 123184-37-2; **5t**, 104568-69-6; **5u**, 123184-88-3; **5v**, 123184-38-3; **5w**, 123184-39-4; **5x**, 123184-40-7; **5y**, 123184-41-8; **5z**, 104568-91-4; **5aa**, 104568-69-6; **5bb**, 123184-42-9; **5cc**, 123184-43-0; **5dd**, 123184-44-1; **5ee**, 123184-45-2; **5ff**, 123184-46-3; **5gg**, 123184-47-4; **5hh**, 123184-48-5; **5ii**, 123184-49-6; **5jj**, 123184-50-9; **6a**, 123184-51-0; **6b**, 123184-52-1; **6c**, 123184-53-2; **6d**, 123184-54-3; **6e**, 123184-55-4; **6f**, 123184-56-5; **6g**, 123184-57-6; **6h**, 123184-58-7; **6i**, 123184-59-8; **6j**, 123184-60-1; **6k**, 123184-61-2; **6l**, 123184-62-3; **6m**, 123184-63-4; **6n**, 123184-64-5; **6o**, 123184-65-6; **6p**, 123184-66-7; **6q**, 123184-67-8; **6r**, 123184-68-9; **6s**, 123184-69-0; **6t**, 104568-70-9; **6u**, 123184-70-3; **6v**, 123184-71-4; **6w**, 123184-72-5; **6x**, 123184-73-6; **6y**, 123184-74-7; **6z**, 123184-75-8; **6aa**, 123184-76-9; **6bb**, 123184-77-0; **6cc**, 123184-78-1; **6dd**, 123184-79-2; **6ee**, 123184-80-5; **6ff**, 123184-81-6; **6gg**, 123184-82-7; **6hh**, 123184-83-8; **6ii**, 123184-84-9; **6jj**, 123184-85-0; **7a**, 123184-90-7; **7b**, 123184-91-8; **7c**, 123184-92-9; **7d**, 123184-93-0; **7e**, 123184-94-1; **7f**, 123184-95-2; **7g**, 123184-96-3; **7h**, 123184-97-4; **7i**, 123184-98-5; **7j**, 123184-99-6; **7l**, 123185-00-2; **7m**, 123185-01-3; **7o**, 123185-02-4; **7q**, 123185-03-5; **7r**, 123185-04-6; **7s**, 123185-05-7; **7t**, 123185-06-8; **7u**, 123185-07-9; **7w**, 123185-08-0; **7x**, 104568-71-0; **7y**, 123185-09-1; **7z**, 123185-10-4; **7aa**, 123185-11-5; **7bb**, 123185-12-6; **7cc**, 123185-13-7; **7dd**, 123185-14-8; **7ee**, 123185-15-9; **7ff**, 123185-16-0; **7gg**, 123185-17-1; **7hh**, 123185-18-2; **7ii**, 123185-19-3; **7jj**, 123185-20-6; **7kk**, 123185-21-7; **7ll**, 123185-22-8; **7mm**, 123185-23-9; **7nn**, 123185-24-0; **8a**, 123185-25-1; **8b**, 123185-26-2; **8c**, 123185-27-3; **8d**, 123185-28-4; **8e** (stereoisomer 1), 123185-29-5; **8e** (stereoisomer 2), 123185-49-9; **8f**, 104568-74-3; 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2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride, 123184-18-9; 3-aminopropionitrile $^1/_2$-fumarate, 2079-89-2; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethanol, 123184-86-1; 2-[2-(4-fluorophenyl)-5-(1,1-dimethylethyl)-1*H*-pyrrol-1-yl]-2-ethyl methanesulfonate, 123184-87-2; methyl acetoacetate, 105-45-3; cholesterol, 57-88-5.

Supplementary Material Available: CAMSEQ-II energies calculated for individual conformations of θ for compounds appearing in Table IV. The data are plotted in Figure 2. Also, a description of the format of a CAMSEQ-II MOL file, followed by MOL files giving x, y, z coordinates for the conformations of compounds I, III, and **8x** used in the pharmacophore model (7 pages). Ordering information is given on any current masthead page.

Inhibitors of Cholesterol Biosynthesis. 2. 1,3,5-Trisubstituted [2-(Tetrahydro-4-hydroxy-2-oxopyran-6-yl)ethyl]pyrazoles

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A series of 1,3,5-trisubstituted pyrazole mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. Since previous studies suggested that the 5-(4-fluorophenyl) and 3-(1-methylethyl) substituents afforded optimum potency, attention was focused on variations in position 1 of the pyrazole ring. Biological evaluation of analogues bearing a variety of 1-substituents suggested that, although most substituents were tolerated, none afforded an advantage over phenyl, which exhibited potency comparable to that of compactin in vitro.

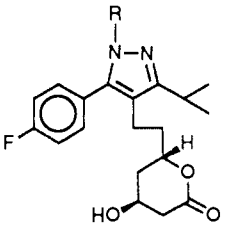
We previously described a series of 2,5-disubstituted pyrrole mevalonolactones whose 3,5-dihydroxyheptanoic acid derivatives were shown to possess varying degrees of intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity in vitro.[1] Structure–activity relationships (SAR) for this series of compounds were determined, and the preferred substituents in the 2- and 5-positions of the pyrrole nucleus were found to be 4-fluorophenyl and 1-methylethyl, respectively. This paper describes the synthesis and biological activity of a series of 1,3,5-trisubstituted pyrazole mevalonolactones[2] with

(1) Roth, B. D.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. Submitted to *J. Med. Chem.*

(2) During the course of this study, a series of trisubstituted pyrazole mevalonolactones were reported to inhibit HMG-CoA reductase by J. R. Wareing at Sandoz Pharmaceuticals Corp. U.S. Patent. 4613610.

0022-2623/90/1833-0031$02.50/0

Table I. Physical Properties and in Vitro HMG-CoA Reductase Inhibitory Actives of Pyrazole Mevalonolactones I

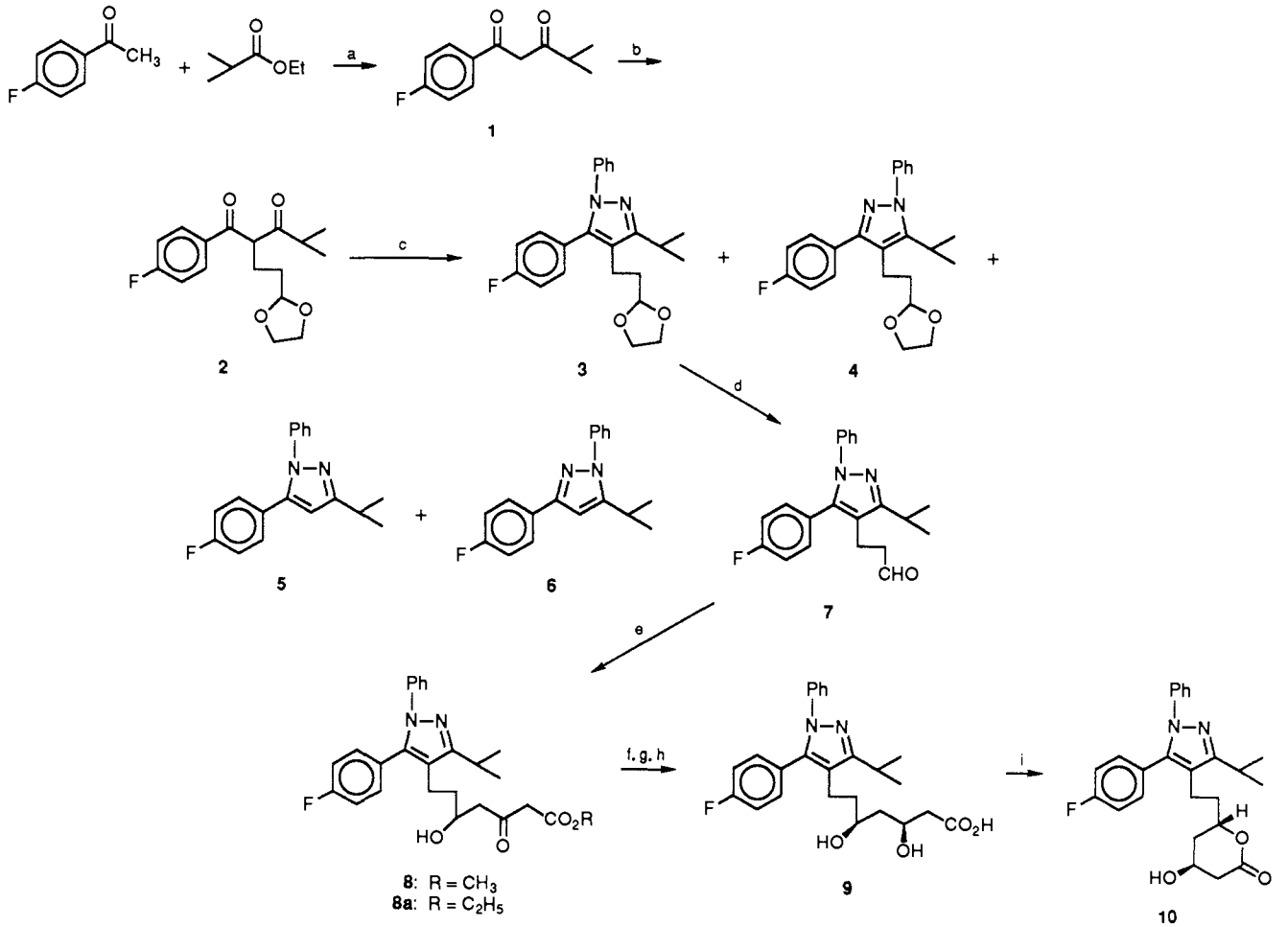


I

no.	R	mp, °C	formula[a]	method of prep	CSI IC_{50},[f,g] μM	rel (CSI) potency[b]
10	Ph	165–167	$C_{25}H_{27}FN_2O_3$	A, B	0.035	83.0
25	4-fluorophenyl	138–142	$C_{25}H_{26}F_2N_2O_3$	A	0.032	62.0
26	4-methylphenyl	152–153	$C_{26}H_{29}FN_2O_3$	A	0.040	49.0
27	4-tolylsulfonyl	foam	$C_{26}H_{29}FN_2O_5S$	B	0.660	4.5
28	4-methoxyphenyl	134–139	$C_{26}H_{29}FN_2O_4$[c]	A	0.039	75.8
29	benzyl	145–148	$C_{28}H_{29}FN_2O_3$[d]	A	0.158	12.6
30	1-naphthyl	75–81	$C_{29}H_{29}FN_2O_3$[e]	B	0.234	19.6

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Potency of compactin arbitrarily assigned a value of 100, and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [c] Anal. Calcd: C, 69.01. Found: C, 68.30. >98% pure by HPLC. [d] Anal. Calcd: H, 6.70. Found: H, 7.22, Calcd: N, 6.42. Found: N, 5.85. >98% pure by HPLC. [e] Anal. Calcd: C, 73.21. Found: C, 72.46. >98% pure by HPLC. [f] Cholesterol synthesis inhibition (CSI). Assays of each inhibitor concentration were performed in triplicate and the precision for compactin was 37%. See ref 1. [g] All compounds tested had a diastereomeric purity of >95% of the trans diastereomer as determined by HPLC and/or 200-MHz NMR.

Scheme I[a]



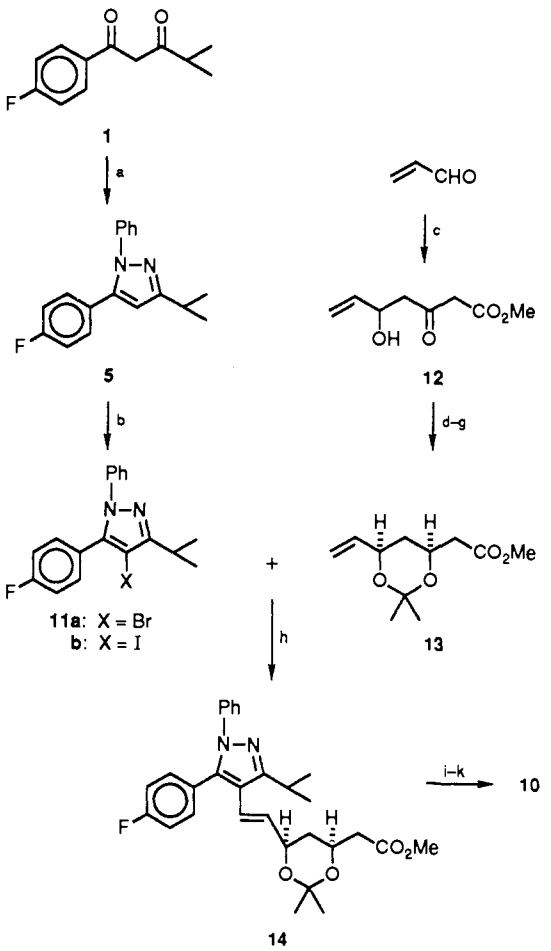
[a] (a) NaH, DMF, 80 °C; (b) NaH, DMF, NaI, $BrCH_2CH_2\overline{CHO(CH_2)O}$; (c) $PhNHNH_2$, AcOH, room temperature; (d) 70% aqueous AcOH, Δ; (e) $^-CH_2CO^-CHCO_2R$; (f) BR_3, air; (g) $NaBH_4$, −78 °C; (h) H_2O_2, ^-OH; (i) tol, Δ.

improved inhibitory potencies compared to the pyrrole mevalonolactones.

Chemistry

The target lactones, listed in Table I, were prepared by the general synthetic routes outlined in Schemes I and II. The general method (method A) employed for the construction of the pyrazole nucleus was condensation of a 1,3-dicarbonyl compound with a suitably substituted hydrazine. Two regioisomers can theoretically arise, but by

Scheme II[a]



[a] (a) $PhNHNH_2$, AcOH, room temperature; (b) NBS or NIS, DMF, 0 °C; (c) $^-CH_2CO^-CHCO_2Et$; (d) Bu_3B, air; (e) $NaBH_4$; (f) H_2O_2/OH^-, (g) $(CH_3)_2C(OCH_3)_2$, CSA, acetone; (h) $(Ph_3P)_2PdCl_2$, Et_3N, DMF, 70 °C; (i) H_2, Pd/C; (j) HCl, NaOH; (k) Tol, Δ.

judicial choice of solvent and reaction temperature, one regioisomer can predominate. Initial studies began with the incorporation of the preferred substituents (4-fluorophenyl and isopropyl) discovered in the SAR of the pyrrole mevalonolactones.[1] The requisite 1,3-diketone **1** was synthesized by a Claisen type acylation of 4-fluoroacetophenone with ethyl isobutyrate.[3] This product, which was almost completely enolized (86% by NMR), was alkylated with 2-(2-bromoethyl)-1,3-dioxolane[4] to give the C-alkylated 1,3-diketone **2** in 58% yield, together with a small amount of material presumed to be the O-alkylated product. Condensation with phenylhydrazine in acetic acid at room temperature afforded predominantly one regioisomer (~90%), tentatively assigned structure **3** in which the aryl groups exist in a 1,5-relationship (rather than 1,3). NMR studies[5] on 1,3- and 1,5-diphenylpyrazoles have shown that the chemical shifts of phenyl groups in the 1,3-regioisomer extend from δ 7.0 to 8.1 ppm. In our case, downfield resonances at δ 8.0 ppm were barely discernible. The majority of the aryl proton resonances were found in the region from δ 7.0 to 7.3 ppm which was in accordance with resonances published for 1,5-diphenylpyrazole. This regiochemistry was confirmed by an X-ray crystallographic analysis of the eventual target lactone derived from **3** (vide supra).[6] An ORTEP drawing of the solid-state conformation of compound **10** is shown in Figure 1. Increased amounts of the 1,3-regioisomer **4** were obtained by changing the reaction solvent to absolute ethanol or by raising the reaction temperature (regardless of solvent choice). Using either (4-chlorophenyl)hydrazine or (4-fluorophenyl)-hydrazine in absolute ethanol at reflux, the regioisomer ratio of pyrazoles obtained was 5:1 (1,5:1,3), this ratio was improved (~10:1) by changing solvent to acetic acid. Also isolated from this reaction was an oil later identified by NMR and independent synthesis[7] as a 5:1 mixture of pyrazole regioisomers **5** and **6** which was presumably derived from the O-alkylated material present from the previous reaction.

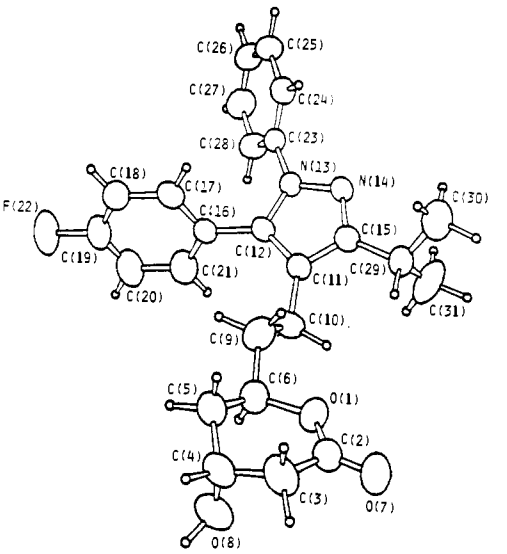


Figure 1. ORTEP view of lactone **10**. Solid-state conformation and crystallographic atom numbering scheme; small circles denote hydrogen atoms.

Acidic hydrolysis of the acetal **3** provided aldehyde **7**, which was condensed with the dianion of methyl acetoacetate.[8] Reduction of the resulting δ-hydroxy-β-keto ester **8** was achieved by the boron chelation method of Narasaka and Pai.[9] Thus, compound **8** was complexed with tri-*n*-butylborane prior to treatment with sodium borohydride. The resulting boronate ester was hydrolyzed with 30% hydrogen peroxide and base to give a mixture of syn (**9**) and anti 1,3-dihydroxy acids, which were lactonised in refluxing toluene with azeotropic removal of water to give predominantly the trans lactone **10** in good yield. HPLC analysis of the lactone **10** showed that the stereoselectivity achieved (3.3:1 trans:cis diastereomers) was not as high as that achieved in the pyrrole series (10:1 trans:cis).[1] No improvement in stereoselectivity was found on addition of an extra equivalent of *n*-Bu_3B, ruling out the possibility of competitive chelation with the pyrazole free nitrogen atom; thus the reason for this lack of stereoselectivity in the pyrazole series remains unclear. Excellent stereoselectivity (>20:1 trans:cis) was achieved by employing triethylborane as chelating agent with pivalic acid catalysis and methanol as cosolvent.[10]

An alternative route (Scheme II) was devised in which the key step was the palladium-catalyzed vinylation of a

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(4) Buchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
(5) Ruu, T.; LeStrat, G. *Bull. Soc. Chem. Fr.* **1975**, *5–6*, 1375.
(6) Prof. A. T. McPhail. Personal communication.
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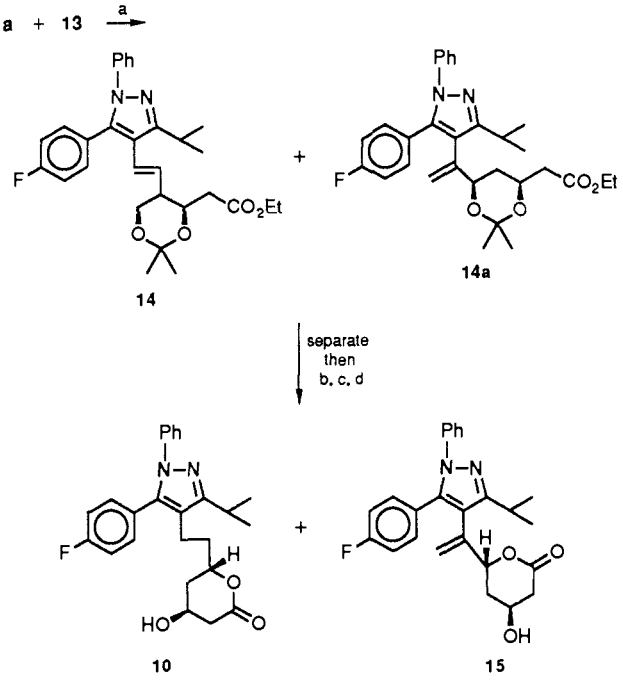
(8) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1981**, *96*, 1082.
(9) (a) Narasaka, K.; Pai, H. C. *Chem. Lett.* **1980**, 1415. (b) Ibid. *Tetrahedron* **1984**, *40*, 2233.
(10) Verhoeven, T. R. *Eur. Pat.* 0164, 049, 1985.

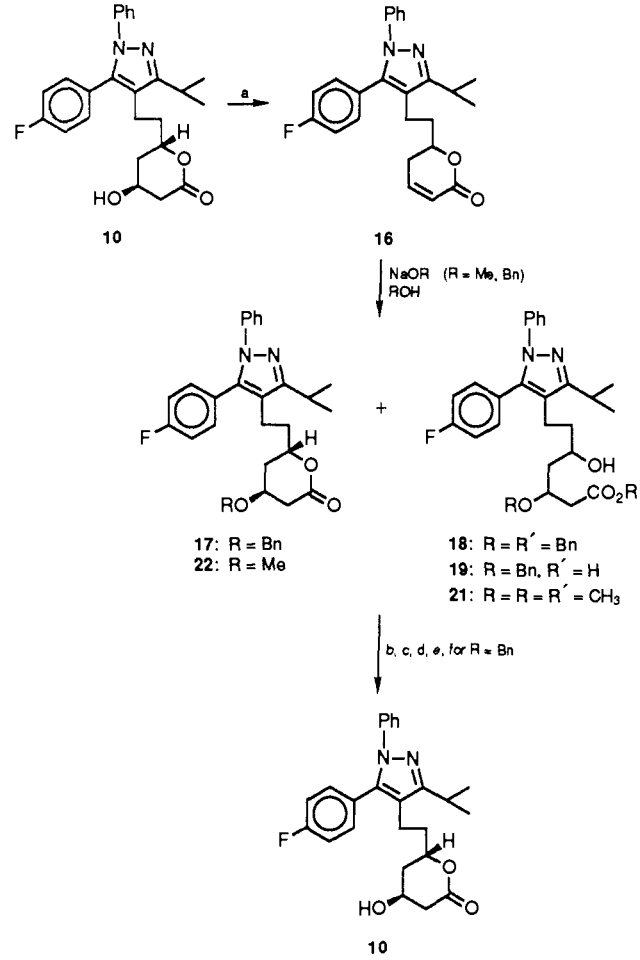
Scheme III



[a] (a) $(PPh_3)_2PdCl_2$, DMF, Et_3N; (b) H_2, Pd/C; (c) HCl, NaOH; (d) Tol, Δ, $-H_2O$.

halopyrazole (**11a,b**) with the intact lactone side chain (**13**).[11] This route had the advantages of being convergent and providing products of satisfactory stereochemical purity (method B). The heterocyclic halides **11a,b** were prepared by condensation of 1,3-diketone **1** with phenylhydrazine in acetic acid at room temperature followed by halogenation of the resulting pyrazole **5** with either NBS or NIS in DMF at 0 °C. The alkene portion (**13**) was constructed via aldol condensation of acrolein with the dianion of methyl (or ethyl) acetoacetate,[12] reduction as before gave the diol, which was protected as the acetonide **13** (25:1 trans:cis diastereomers). Although treatment of **11a** with **13** under the standard conditions described by Heck[11] did in fact provide a modest (50%) yield of **14**, this reaction proved capricious. A variety of catalysts were employed (e.g., $(Ph_3P)_2PdCl_2$, $Pd(OAc)_2$, 10% Pd/C, polymer-supported catalysts, etc.), and it was concluded that 2–6 mol % of $(Ph_3P)_2PdCl_2$ was the preferred catalyst. A number of bases (e.g., tri-*n*-butylamine, diisopropylethylamine, and triethylamine) and solvents (e.g., DMF and acetonitrile) were examined, and the best yields were obtained with triethylamine and DMF as solvents. Changing the heterocyclic halide from bromide (**11a**) to iodide (**11b**) gave increased amounts of the dehalogenated pyrazole **5**. Although it has been reported that use of a more hindered phosphine ligand on the catalyst reduces this side reaction, replacement of $(Ph_3P)_2PdCl_2$ with $[(o\text{-}CH_3Ph)_3P]_2PdCl_2$ provided no improvement in yield.[11] The 200-MHz NMR showed the formation of predominantly the trans alkene **14** (J_{trans} = 15 Hz). A minor product was produced by addition to the more substituted carbon atom of the double bond (Scheme III), giving the olefin **14a**. This structure was confirmed by HETCOR NMR[13] on the resulting lactone **15**. Catalytic reduction of olefin **14**, removal of the protecting groups, and lactonization afforded lactone **10** as a mixture of diastereomers (64:1 trans:cis).

Scheme IV[a]

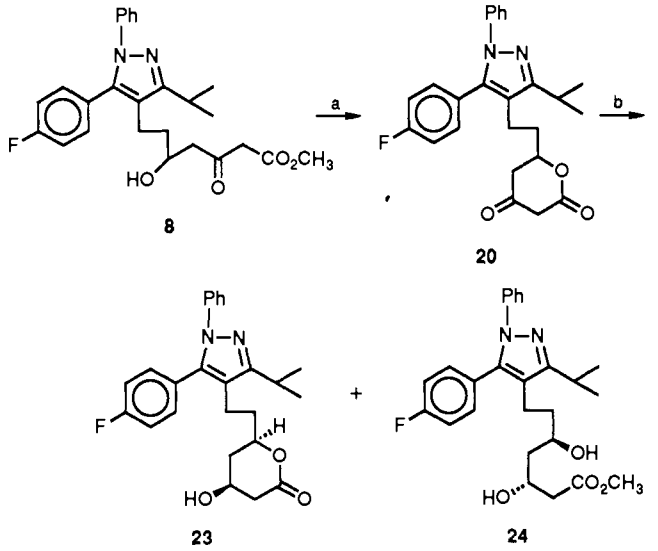


[a] (a) Ac_2O, DBU, CH_2Cl_2; (b) NaOH, (c) H^+; (d) H_2, Pd/C, EtOAc; (e) Tol, Δ.

In order to avoid the very low temperature reduction of compound **8** in Scheme I and the capricious nature of the Heck reaction shown in Scheme II, an alternative synthesis was devised in which the required 1,3-asymmetry was introduced by the stereospecific 1,4-conjugate addition of an alkoxide.[14] Thus, elimination of water from the mixture of lactone diastereomers **10** produced by borohydride reduction or from the cis lactone **23** obtained from the catalytic reduction of compound **20** produced the $\Delta^{\alpha,\beta}$-unsaturated lactone **16** in 68% yield (Scheme IV). Addition of sodium benzylate in benzyl alcohol afforded a mixture of products thought to consist mainly of compounds **17** and **18**. After base hydrolysis the mixture was acidified to predominantly hydroxy acid **19**. This material was then hydrogenated over 10% Pd/C and the resulting material lactonized to give compound **10** as a mixture of diastereomers (8:1 trans:cis by HPLC). In a similar fashion, sodium methoxide was added to lactone **16** to give, after base hydrolysis, acidification, and lactonization, the 4-methoxy lactone **22** as a mixture of diastereomers (7.4:1 trans:cis by HPLC). The cis diastereomer **23** was obtained as the predominant product by catalytic hydrogenation of ketone **20**, which was prepared by base hydrolysis of compound **8** (Scheme V). Catalytic reduction of compound **20** gave, after chromatography, a mixture of ester **24** and lactone **23** (4:1 cis:trans diastereomers).

(11) Heck, R. F. *Org. React. (N.Y.)* **1982**, *27*, 345.
(12) Brussani, G.; Ley, S. V.; Wright, J. L.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 303.
(13) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350.
(14) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, 1255–58.

Scheme V[a]



[a] (a) NaOH then H^+; (b) 10% Ru-C, H_2, MeOH, room temperature.

Table II. In Vitro Inhibitory Potencies against HMG-CoA Reductase

no.	CSI IC_{50},[a,c] μM	rel potency[b]
15	17.8	0.17
20	10.0	0.32
22	3.16	1.00
23	0.7	4.40

[a] Cholesterol synthesis inhibition (CSI). Assays of each inhibitor concentration were performed in triplicate and the precision for compactin was 37%. See ref 1. [b] Potency of compactin arbitrarily assigned a value of 100, and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. See ref 1. [c] The diastereomeric purities of compounds **22** and **23** are indicated in the Experimental Section. Compound **15** had a diastereomeric purity of >95% of the trans diastereomer as indicated by 200-MHz NMR.

Biological Results

The target lactones and related compounds listed in Tables I and II were saponified to the hydroxy acids and tested for their ability to inhibit the enzyme HMG-CoA reductase by employing a crude liver homogenate derived from rats fed a chow diet containing 5% cholestyramine.[1,15] This screen was designated CSI (cholesterol synthesis inhibition screen). The biological activities are displayed in Tables I and II as an IC_{50} (i.e., the concentration needed to inhibit enzyme activity by 50%). Compactin was employed as the internal standard in each testing protocol.

The optimum distance between the lactone and the heterocyclic ring in the pyrrole series was achieved by a two-carbon bridging unit.[1] This feature was incorporated in all the pyrazole derivatives described here apart from compound **15**, in which the pyrazole and lactone portions are separated by only one carbon atom. This compound is relatively inactive.

Modification of the lactone portion generally decreases the activity and confirms the strict structural requirements found by others.[16] Methyl ether **22** exhibited about $^1/_{100}$ potency of compactin whereas the racemic hydroxy compound **10** was nearly equipotent; if resolved, this compound would be expected to be more potent than compactin. The keto analogue **20** also exhibited low potency.[17] The cis lactone stereoisomer **23** (a 4:1 mixture of cis:trans diastereomers by HPLC) also displayed significantly reduced biological activity.[16] The residual biological activity was probably due to the presence of the trans diastereomer.

As previous studies suggested that the 5-(4-fluorophenyl) and 3-(1-methylethyl) substituents afforded optimum potency, we focused our attention on variations in position 1 of the pyrazole ring. A number of (para-substituted phenyl)hydrazines were employed, and it was demonstrated that in the limited series of compounds prepared, varying the electronic distribution in the phenyl ring did not, in general, have deleterious effects on in vitro potency. Electron-withdrawing, e.g., **25**, and electron-donating, e.g., **26** and **28**, groups were equally tolerated; however, compound **27**, which has a hydrophilic electron-withdrawing group present, was considerably less potent. Replacement by naphthyl (e.g., **30**) caused a significant decrease in potency as did replacement by an alkyl group, e.g., **29**.

Conclusion

A small series of pyrazole mevalonolactones were prepared and evaluated for their ability to inhibit the enzyme HMG-CoA reductase in vitro. By focusing on compounds possessing the 5-(4-fluorophenyl)-3-(1-methylethyl) substitution found to be optimum in previous studies, a compound (**10**) was rapidly identified that was almost equipotent to compactin. Additional modification of the 1-phenyl ring of **10** did not improve activity in vitro.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet MX-1 FT-IR spectrophotometer. Nuclear magnetic resonance spectra were determined on either a Varian EM-390 or a Varian XL-200 spectrometer. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer. HPLC analyses were performed on a Varian 5500 HPLC with a UV 200 detector (wavelength was 251 nm). The detailed protocol of the biological assay is described in ref 1.

1-(4-Fluorophenyl)-4-methyl-1,3-pentanedione (1). A mixture of 4-fluoroacetophenone (150 g, 1.09 mol) and ethyl isobutyrate (126 g, 1.09 mol) in dioxane (1.5 L) was added dropwise under a nitrogen atmosphere to a vigorously stirred suspension of hexane-washed sodium hydride (133 g, 58.8% NaH, 3.25 mol) in dioxane (3.0 L). Vigorous evolution of gas ensued, after which the mixture was heated to 80–90 °C for 4 h. The mixture was then allowed to cool to room temperature, after which it was poured into ice-cold 2 M hydrochloric acid (6 L) with vigorous stirring and extracted with ethyl acetate (4 × 1 L). The combined ethyl acetate extracts were washed with water (2 × 500 mL) and brine (2 × 500 mL) and dried ($MgSO_4$). The solution was filtered and the filtrate concentrated under vacuum. Distillation of the residue yielded compound 1: bp 100–110 °C/1 mm (116 g, 50%); ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.30 (s, 3 H), 2.60 (m, 1 H, J = 7 Hz), 6.1 (s, 1 H), 7.15 (m, 2 H), 7.9 (m, 2 H), and 16.2 (br s, 1 H) ppm. IR (thin film) 2973, 2825, 1653, 1603, 1578, 1509, 1462, 1240, 1160, 1089, 851, and 793 cm^{-1}. Anal. ($C_{12}H_{13}FO_2$) C, H, F.

2-[2-(1,3-Dioxolan-2-yl)ethyl]-1-(4-fluorophenyl)-4-methyl-1,3-pentanedione (2). To a suspension of hexane-washed sodium hydride (22.8 g, 58% NaH, 0.56 mol) in anhydrous dimethylformamide (DMF) (750 mL) was added dropwise, with

(15) Dugan, R.; Slakey, L. L.; Briedis, A. V.; Porter, J. W. *Arch. Biochem. Biophys.* **1972**, *152*.
(16) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
(17) One possible explanation for this lack of activity may have been that during the biological assay procedure, base treatment of compound **20** may not have produced the open acid form. We thank the reviewer for this suggestion.

vigorous stirring under a nitrogen atmosphere, a solution of **1** (116 g, 0.56 mol) in anhydrous DMF (450 mL). Vigorous effervescence ensued. When gas evolution had ceased, sodium iodide (21.0 g, 0.14 mol) was added, followed by the dropwise addition of 2-(2-bromoethyl)-1,3-dioxolane[4] (100.9 g, 0.56 mol) in anhydrous DMF (450 mL). The resulting mixture was heated at 80–90 °C for 36 h after which it was cooled to room temperature and poured into ice–water (2 L). This was extracted with ethyl acetate (4 × 1 L), and the combined organic extracts were washed successively with water (500 mL) and brine (500 mL) and dried ($MgSO_4$). The solution was filtered and the filtrate was concentrated under vacuum. The residue was flash chromatographed on silica gel, eluting with 25% ethyl acetate–hexane to yield **2** (100 g, 58%); ^1H NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.15 (s, 3 H), 1.7 (m, 2 H), 2.2 (m, 2 H), 2.8 (m, 1 H), 3.9 (m, 4 H), 4.7 (t, 1 H), 4.9 (t, 1 H), 7.2 (m, 2 H), and 8.1 (m, 2 H) ppm; IR (thin film) 2972, 1723, 1676, 1600, 1509, 1411, 1237, 1160, and 1037 cm^{-1}. Anal. ($C_{17}H_{21}FO_4$) C, H, F.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (3). To solution of **2** (104.75 g, 0.34 mol) in absolute ethanol under nitrogen (1 L) was added dropwise, with stirring, phenylhydrazine (40.45 g, 0.374 mol). When addition was complete, the solution was heated under reflux for 5 days[18] and then cooled to room temperature. The solution was concentrated under vacuum and chromatographed on silica gel. Elution with 15% ethyl acetate–hexane gave a yellow oil (9.7 g, R_f 0.55 (15% EtOAc–hexane)) identified by NMR and synthesis as a 5:1 mixture of regioisomers **5** and **6**. Further elution gave a 10:1 regioisomer mixture of pyrazoles **3** and **4** (NMR shows two sets of isopropyl methyl groups at δ 1.4 and 1.2 ppm in a 10:1 ratio). This mixture solidified and was recrystallized (hexane) to give **3**: mp 98–100 °C (hexane) (50.85 g, 40%); ^1H NMR ($CDCl_3$) δ 1.4 (s, 3 H), 1.35 (s, 3 H), 1.8 (m, 2 H), 2.7 (m, 2 H), 3.1 (t, 1 H), 3.9 (m, 4 H), 4.8 (t, 1 H), and 7.2 (m, 9 H) ppm; IR (KBr) 2950, 2900, 1596, 1566, 1511, 1440, 1377, 1227, 1158, 1143, 1058, 970, and 842 cm^{-1}. Anal. ($C_{23}H_{25}FN_2O_2$) C, H, N.

3(or 5)-(4-Fluorophenyl)-5(or 3)-(1-methylethyl)-1-phenyl-1*H*-pyrazoles (5 and 6). To a solution of **1** (1 g, 0.0048 mol) in absolute ethanol (10 mL) was added via a syringe, with stirring, phenylhydrazine (0.52 mL, 0.0053 mol). The solution was heated to reflux for 24 h and then cooled to room temperature. The solution was concentrated under vacuum and then chromatographed on silica gel. Elution with 5% ethyl acetate–hexane gave a yellow oil (1.1 g, R_f 0.24 (5% EtOAc–hexane)) identified by NMR as a 5:1 regioisomer mixture of **5** and **6**. The oil solidified and was recrystallized (hexane) to give a 5:1 mixture of regioisomers: mp 67–70 °C (0.5 g, 37%); ^1H NMR ($CDCl_3$) δ 1.2 (d, 6 H, $(CH_3)_2CH$, regioisomer (6) (ht = 1)), 1.3 (d, 6 H, $(CH_3)_2CH$, regioisomer (5) (ht = 5), 3.1 (m, 1 H), 6.35 (s, 1 H, 4 H regioisomer (5) (ht = 5)), 6.5 (s, 1 H, 4 H regioisomer (6) (ht = 1)) and 6.9–7.4 (m, 9H) ppm; IR (KBr) 3450, 3053, 2964, 1594, 1510, 1440, 1374, 1302, 1222, 1164, 996, and 849 cm^{-1}. Anal. ($C_{18}H_{17}FN_2$) C, H, N.

5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole-4-propanal (7). A solution of **3** (50.85 g, 0.134 mol) in 70% aqueous acetic acid (1.0 L) was heated under reflux for 48 h with stirring. The solution was then cooled to room temperature and partitioned between ethyl acetate (1.0 L) and water (1.0 L). The phases were separated, and the aqueous phase was reextracted with ethyl acetate (1.0 L). The combined organic layer was washed successively with saturated sodium bicarbonate solution (250 mL), water (250 mL), and brine (250 mL). The ethyl acetate solution was dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was flash chromatographed on silica gel, eluting with 15% ethyl acetate–hexane. The eluted material solidified and was recrystallized (hexane) to give **7**: mp 86–88 °C (hexane) (29.0 g, 65%); ^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.35 (s, 3 H), 2.4 (t, 2 H), 2.7 (t, 2 H), 3.05 (m, 1 H), 7.2–7.6 (m, 9 H), and 9.6 (s, 1 H) ppm. IR (KBr) 2961, 2869, 1728, 1609, 1598, 1498, 1439, 1376, 1334, 1224, 1159, 971, 840, and 767 cm^{-1}. Anal. ($C_{15}H_{17}FN_2O$) H, N; C: calcd, 69.21; found, 68.51.

(±)-Methyl 5-(4-Fluorophenyl)-δ-hydroxy-3-(1-methylethyl)-β-oxo-1-phenyl-1*H*-pyrazole-4-heptanoate (8). Methyl acetoacetate (11.48 mL, 0.106 mol) in anhydrous THF (100 mL) was added dropwise to a stirred suspension of sodium hydride (58.8% oil suspension, 4.56 g, 0.116 mol) in anhydrous THF (100 mL) at 0 °C under an N_2 atmosphere. When gas evolution was complete, a 2.6 M solution (40.9 mL, 0.106 mol) of *n*-butyllithium in hexane was added over 30 min. The resulting solution was stirred for an additional 60 min at 0 °C and then cooled to −78 °C (dry ice/acetone). This was then treated with a solution of **7** (23.8 g, 0.0709 mol) in anhydrous THF (100 mL) added dropwise over 60 min. The resulting orange solution was stirred 30 min at −78 °C and then at 0 °C for an additional 30 min before quenching with glacial acetic acid (35 mL) and 2 M aqueous HCl (70 mL) with vigorous stirring. The resulting mixture was then partitioned between diethyl ether (750 mL) and water (250 mL). After separation of phases, the aqueous layer was reextracted with diethyl ether (200 mL), and the combined organic extracts were washed successively with 0.2 M HCl (200 mL), water (200 mL), saturated sodium bicarbonate solution (3 × 150 mL), and brine (200 mL). The ether solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield a yellow oil, which was then flash chromatographed on silica gel. Elution with 40% ethyl acetate gave **8** (32.3 g, 84%): ^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.4 (s, 2 H), 1.45 (m, 2 H), 2.47 (d, 2 H), 2.7 (m, 2 H), 3.1 (m, 1 H), 3.6 (s, 3 H), 3.38 (s, 2 H), 3.9 (m, 1 H), and 6.8–7.2 (m, 9 H) ppm. The ethyl ester **8a** was also synthesized in comparable yield with ethyl acetoacetate: ^1H NMR ($CDCl_3$) δ 1.27 (t, 3 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 1.45 (m, 2 H), 2.6 (d, 2 H), 2.4–2.7 (m, 2 H), 3.1 (m, 1 H), 3.4 (s, 2 H), 3.9 (m, 1 H), 4.2 (q, 2 H), and 7.0–7.2 (m, 9 H) ppm; IR (thin film) 2965, 1743, 1714, 1654, 1599, 1559, 1512, 1500, 1374, 1227, 1160, and 844 cm^{-1}; HPLC indicated, 100% purity (retention time 23.2 min). Anal. ($C_{26}H_{29}FN_2O_4$) C, H; N: calcd, 6.19; found, 5.73.

(±)-*trans*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10). (i) Use of Tri-*n*-butylborane and Air Activation. Through a THF (150 mL) solution of tri-*n*-butylborane (76.5 mL, 1 M, 0.076 mol) and **8** (31.48 g, 0.070 mol) was bubbled air (125 mL), and the solution was stirred at room temperature under a nitrogen atmosphere for 24 h. The solution was then cooled to −78 °C, and sodium borohydride (3.15 g, 0.0835 mol) was added in one portion. The mixture was allowed to warm to −20 °C over 2 h and then to 0 °C where it was stirred for 1 h. The reaction was then quenched by the addition of glacial acetic acid (14.6 mL, 0.205 mol) and water (17 mL). When gas evolution had ceased, 2 N sodium hydroxide (167 mL) was added followed by the dropwise addition of 30% hydrogen peroxide (25.7 mL, 0.25 mol) over 1 h. The resulting mixture was allowed to warm to room temperature overnight and then partitioned between ether (500 mL) and water (500 mL). The aqueous layer was separated and the ether layer was washed with 3 N NaOH (2 × 200 mL). The combined aqueous layers were then cooled to 0 °C and acidified with ice-cold 6 N HCl. This was then extracted with ethyl acetate (4 × 200 mL). The combined organic extracts were then washed with water (200 mL) and brine (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to yield **9** (30 g, 95%) as a mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racemates. This material was dissolved in toluene (500 mL) and heated under reflux with azeotropic removal of water for 3 h. The mixture was cooled to room temperature and concentrated in vacuo. The residue was flash chromatographed on silica gel, eluting with 75% ethyl acetate–hexane to produce **10** (16.6 g, 60%) as a colorless solid: mp 157–159 °C (5:1 cyclohexane:chloroform).

^1H NMR ($CDCl_3$) δ 1.3 (s, 3 H), 1.4 (s, 3 H), 1.6–1.9 (m, 4 H), 2.2 (br s, 1 H), 2.5–2.8 (m, 4 H), 3.1 (m, 1 H), 4.3 (m, 1 H), 4.6 (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 3400, 2962, 2868, 1707, 1598, 1511, 1440, 1376, 1252, 1225, 1052, 972, 843, and 767 cm^{-1}.

HPLC (stationary phase, Altex C 18 column; mobile phase, 50:50 0.05 M citric acid (pH = 4.0)/CH_3CN) indicated a 3.3:1 mixture of trans (t_R = 13.1 min)/cis (t_R = 12.0 min) diastereomers. Anal. ($C_{25}H_{27}FN_2O_3$) C, H, N. The cis diastereomer was visible by NMR; the H6 and H4 protons appeared as a broad multiplet at δ 4.1 ppm.

(ii) Use of Triethylborane with Pivalic Acid Catalysis. To a room temperature solution of triethylborane (2.5 mL of a 1 M THF solution (0.00214 mol)) under a nitrogen atmosphere

(18) Use of acetic acid as solvent greatly reduces reaction times.

was added, with stirring, a catalytic amount of pivalic acid (0.022 g, 0.000 21 mol). The resulting solution was stirred at room temperature for 1 h before a THF (7 mL) solution of **8a** (1 g, 0.002 14 mol) was added dropwise. The resulting solution was stirred at room temperature for a further 1 h before cooling to −78 °C. Methanol (1 mL) was added followed by the addition of sodium borohydride (0.0893 g, 0.002 36 mol) in one portion. Vigorous gas evolution ensued. This mixture was stirred at −78 °C for 2.5 h. It was then poured into an excess of ice-cold 30% hydrogen peroxide (10 mL) and extracted with ethyl acetate. The organic layer was then washed extensively with water and brine, dried ($MgSO_4$), filtered, and evaporated to yield 1.0 g of the corresponding 1,3-diol (quantitative) as a 23:1 mixture of 3*R*,5*R*/3*S*,5*S*; and 3*S*,5*R*/3*R*,5*S* racemates. (HPLC indicated that the 3*R*,5*R*/3*S*,5*S* racemate had a retention time of 13.5 min and the 3*R*,5*R*/3*R*,5*S* racemate had a retention time of 11.7 min.)

5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (5). To a solution of **1** (10.6 g, 0.0509 mol) in glacial acetic acid (100 mL) was added at room temperature phenylhydrazine (6.04 g, 0.0559 mol). The mixture was stirred overnight at room temperature and then poured into ice-cold saturated aqueous sodium bicarbonate (200 mL). An oil precipitated, which then crystallized. These crystals were collected and redissolved in hexane. The hexane solution was washed with water (100 mL) and brine (100 mL) and then dried ($MgSO_4$). The solution was then concentrated to one-quarter of its original volume and cooled to yield **5** as colorless crystals: mp 70–72 °C (hexane) (12.0 g, 84%); ^{1}H NMR δ ($CDCl_3$) 1.34 (s, 3 H), 1.38 (s, 3 H), 3.1 (m, 1 H), 6.3 (s, 1 H), 6.9–7.3 (m, 9 H) ppm; IR (KBr) 3052, 2964, 1594, 1510, 1440, 1374, 1302, 1222, 1164, 1089, 995, and 849 cm^{-1}. Anal. ($C_{18}H_{17}FN_2$) C, H, N.

4-Bromo-5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (11a). *N*-Bromosuccinimide (6.21 g, 0.0348 mol) was added to a solution of **5** (11.3 g, 0.0348 mol) in DMF (130 mL) at 0 °C under a nitrogen atmosphere. After 1 h, a solid was deposited, which was filtered and washed extensively with water. This solid was recrystallized from toluene to yield **11a**: mp 126–128 °C (toluene) (8.1 g, 56%); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.42 (s, 3 H), 3.1 (m, 1 H), 7.0–7.3 (m, 9 H); IR (KBr) 1593, 1551, 1496, 1376, 1304, 1227, 1160, 1109, 1036, 968, and 843 cm^{-1}. Anal. ($C_{18}H_{16}BrFN_2$) C, H, N.

5-(4-Fluorophenyl)-4-iodo-3-(1-methylethyl)-1-phenyl-1*H*-pyrazole (11b). *N*-Iodosuccinimide (4.81 g, 0.0214 mol) was added in one portion to a stirred solution of **5** (5.0 g, 0.0178 mol) in DMF (100 mL) cooled to 0 °C under a dry nitrogen atmosphere. The mixture was allowed to warm to room temperature overnight and then recooled to 0 °C before more *N*-iodosuccinimide (0.24 g, 0.0011 mol) was added. This was then allowed to warm to room temperature and then poured into water (500 mL). This aqueous mixture was extracted with diethyl ether (2 × 250 mL). The ether extracts were diluted with hexane (200 mL) and washed with water (100 mL), 10% aqueous sodium bisulfite (100 mL), and brine (100 mL) and dried ($MgSO_4$). Filtration and concentration afforded **11b** (6.8 g, 94%) as orange/tan needles (mp 141–143 °C) (hexane): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.42 (s, 3 H), 3.1 (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2929, 1600, 1542, 1500, 1460, 1427, 1373, 1298, 1229, 1159, 1028, 968, and 845 cm^{-1}. Anal. ($C_{18}H_{16}FIN_2$) C, H, N.

Methyl 5-hydroxy-3-oxo-6-heptenoate (12) was prepared as described by Ley et al.[12] Ethyl 5-hydroxy-3-oxo-6-heptenoate was prepared similarly in 94% yield: **12**: ^{1}H NMR ($CDCl_3$) δ 1.2 (tr, 3 H), 2.78 (d, 2 H, 4-H, *J* = 6.3 Hz), 3.4 (s, 2 H, 2-H), 4.2 (q, 2 H), 4.6 (dt, 1 H, 5-H, *J* = 6.0, 6.3 Hz), 5.07–5.35 (m, 2 H, 7-H), and 5.88 (ddd, 1 H, 6-H, *J* = 16.3, 10.0, 6.0 Hz) ppm.

Methyl 6-Ethenyl-2,2-dimethyl-1,3-dioxane-4-acetate (13). Air (20 mL) was bubbled through a solution of triethylborane (64 mL, 1 M THF, 0.064 mol) and **12** (10 g, 0.058 mol) in anhydrous THF (50 mL) under a nitrogen atmosphere. The resulting solution was stirred overnight at room temperature and then cooled to −78 °C. Sodium borohydride (2.64 g, 0.0696 mol) was added in one portion, and the vigorously stirred suspension was allowed to warm slowly to 0 °C over 2 h. (Vigorous gas evolution was noticed at −50 °C.) The reaction was quenched by the dropwise addition of glacial acetic acid (15 mL) followed by addition of water (20 mL) and methanol (20 mL). After all the solid had been consumed, saturated aqueous sodium bicarbonate solution (50 mL) was added carefully, followed by the dropwise addition of 30% hydrogen peroxide (19.2 mL). This solution was stirred for 1 h and then poured into ether (800 mL). The organic phase was washed with water (2 × 160 mL) and brine (100 mL). It was dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed on silica gel, eluting with ethyl acetate–hexane (50:50), to give methyl 3,5-dihydroxy-6-heptenoate (7.05 g, 69%) as a mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racemates, which was used in the subsequent step without further purification. This crude mixture (7.0 g, 0.04 mol) was dissolved in a mixture of dichloromethane (100 mL) and 2,2-dimethoxypropane (20 mL, 0.162 mol). A catalytic amount of camphorsulfonic acid (0.05 g) was added and the solution was stirred overnight at room temperature. Concentration and flash chromatography on silica gel (eluting with 25% ethyl acetate–hexane) of the resulting residue gave **13** (4.25 g, 50%) as a 25:1 mixture of 3*R*,5*R*/3*S*,5*S* and 3*S*,5*R*/3*R*,5*S* racemates (HPLC indicated that the 3*R*,5*R*/3*S*,5*S* racemate had a retention time of 8.5 min and the 3*S*,5*R*/3*R*,5*S* racemate had a retention time of 8.4 min): ^{1}H NMR ($CDCl_3$) δ 1.2–1.3 (m, 1 H, 5-H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.60 (m, 1 H, 5-H′), 2.36 (dd, 1 H, *J* = 14, 6 Hz), 2.56 (dd, 1 H, *J* = 14, 6 Hz), 3.6 (s, 3 H), 4.3–4.5 (m, 2 H, 4-H, 6-H), 5.1–5.3 (m, 2 H), 5.8 (m, 1 H) ppm; IR (thin film) 2994, 1743, 1439, 1382, 1316, 1261, 1203, 1170, 1099, 1001, and 926 cm^{-1}. Anal. ($C_{11}H_{18}O_4$) H; C: calcd, 61.66; found, 60.12.

(*E*)-Methyl 6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethenyl]-2,2-dimethyl-1,3-dioxane-4-acetate (14). A solution of **11a** (1.07 g, 0.003 mol), **13** (1.1 g, 0.0051 mol), and bis(triphenylphopshine)palladium(II) chloride (0.042 g, 0.00006 mol, 2 mol %) in 6 mL of a 50:50 mixture of triethylamine and DMF was stirred and heated at reflux overnight under a nitrogen atmosphere. The solution was cooled to room temperature and diluted with ether (100 mL) and washed with water (100 mL), 2 M hydrochloric acid (50 mL), water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (500 mL). The organic extracts were dried ($MgSO_4$), filtered, and evaporated. The residue was flash chromatographed on silica gel, eluting with 10% ethyl acetate–hexane, to give **14** (0.74 g, 50%) as yellow crystals, mp 136–137 °C, together with small amounts of **5**: ^{1}H NMR ($CDCl_3$) δ 1.25–1.6 (m, 14 H), 2.36 (dd, 1 H, *J* = 14, 6 Hz), 2.56 (dd, 1 H, *J* = 14, 6 Hz), 3.20 (m, 1 H), 3.7 (s, 3 H), 4.3 (m, 2 H), 5.7 (dd, 1 H, *J* = 15 Hz, 7 Hz), 6.23 (d, 1 H, *J* = 15 Hz), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2914, 1739, 1663, 1597, 1546, 1510, 1441, 1379, 1276, 1225, 1160, 1078, 974, and 841 cm^{-1}; HPLC indicated a 59:1 mixture of 4*R*,6*R*/4*S*,6*S* and 4*S*,6*R*/4*R*,6*S* racemates (the 4*R*,6*R*/4*S*,6*S* racemate had a retention time of 12.57 min, and the 4*S*,6*R*/4*R*,6*S* racemate had a retention time of 13.87 min). Anal. ($C_{29}H_{33}FN_2O_4$) C, H, N.

(±)-*trans*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (10). A solution of **14** (0.63 g, 0.001 28 mol) in ethyl acetate (10 mL) was hydrogenated under a balloon of hydrogen gas with 10% palladium on charcoal as catalyst at 25 °C for 2 days. The catalyst was then removed by filtration through Celite, and the filtrate was concentrated and redissolved in 50:50 THF/1 M HCl (30 mL). This was stirred for 5 h at room temperature, and then 25% sodium hydroxide was added until the solution was basic (pH ~10). After stirring for 30 min, the mixture was diluted with water and extracted with ether. The aqueous solution was then acidified with 2 M hydrochloric acid and extracted with ethyl acetate. The organic extracts were then washed with brine and dried ($MgSO_4$). Filtration and concentration provided the crude dihydroxy acid, which was lactonized with azeotropic removal of water by refluxing in toluene for 3 h. The cooled solution was concentrated to ca. 10 mL and allowed to stand. Pure lactone **10** crystallized as a white solid (0.35 g, 65%) (mp 163–165 °C, 2× 165–167 °C): HPLC indicated a 64:1 mixture of trans (t_R = 13.4 min)/cis (t_R = 12.3 min) diastereomers. Anal. ($C_{25}H_{27}FN_2O_3$) C, H, N.

(±)-*trans*-6-[1-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (15). A mixture of crude **14** (34 g, 0.067 mol) and 10% Pd/C (1 g) in absolute EtOH (100 mL) was hydrogenated for 2 days at atmospheric pressure and room temperature. The catalyst was removed by filtration through Celite. After concentration, the filtrate residue was dissolved in 3:2:1 THF–2 M

HCl–MeOH (600 mL) and the mixture stirred for 3 days at room temperature. This was made alkaline (25% aqueous NaOH) and partitioned between ether and water. The aqueous layer was then acidified (2 M HCl) and extracted with ethyl acetate (2 × 250 mL). The combined organic extracts were then washed with brine (100 mL), dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in toluene and refluxed with azeotropic removal of water for 2 h. Concentration and flash chromatography on silica gel provided a first fraction identified as **15** (1.5 g, 5.3%; mp 157–158 °C) and a second fraction of **10** (6 g, 22%; mp 156–157 °C): ^1H NMR ($CDCl_3$) δ 1.3 (s, 6 H), 1.5 (m, 1 H), 1.7 (m, 1 H), 2.1 (br s, 1 H), 2.4 (m, 1 H), 2.7 (m, 1 H), 3.1 (m, 1 H), 4.1 (m, 1 H), 4.9 (dd, 1 H), 5.4 (d, 1 H), 5.7 (d, 1 H), and 7.0–7.4 (m, 9 H) ppm; IR (KBr) 2931, 1725, 1642, 1598, 1546, 1510, 1438, 1379, 1229, 1159, 1071, 1045, 975, 845, and 766 cm^{-1}. Anal. ($C_{25}H_{25}FN_2O_3$) C, H, N.

6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]-5,6-dihydro-2*H*-pyran-2-one (16). A solution of **10** (3.3:1 mixture of trans:cis isomers) (20 g, 0.0473 mol) was dissolved in anhydrous dichloromethane (50 mL) under a nitrogen atmosphere. Acetic anhydride (5.3 g, 0.052 mol) and DBU (15.8 g, 0.104 mol) were added dropwise to the solution. The reaction mixture was stirred overnight and then diluted with ether (150 mL) and washed with 2 M HCl (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and brine (100 mL), and dried ($MgSO_4$). Filtration and concentration gave a residue (17 g), which was passed through silica gel. Elution with hexane gave **16** (13 g, 68%) as a white solid (mp 89 °C (hexane)): ^1H NMR ($CDCl_3$) δ 1.36 (d, 6 H), 1.6–1.9 (m, 2 H), 2.2 (m, 2 H), 2.7 (m, 2 H), 3.0 (m, 1H), 4.3 (m, 1 H), 6.0 (dd, 1 H), 6.8 (m, 1 H), and 7.0–7.3 (m, 9 H) ppm; IR (KBr) 2961, 2868, 1723, 1596, 1562, 1511, 1439, 1376, 1336, 1248, 1159, 1094, 1043, 970, and 844 cm^{-1}. Anal. ($C_{25}H_{25}FN_2O_2$) C, H, N.

6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]dihydro-2*H*-pyran-2,4(3*H*)-dione (20). Ethyl acetoacetate (1.14 mL, 0.0089 mol) in anhydrous THF (15 mL) was added dropwise to a stirred suspension of hexane-washed sodium hydride (58.8% oil suspension) (0.225 g) in anhydrous THF (20 mL) at 0 °C under an N_2 atmosphere. When gas evolution was complete, a solution of *n*-butyllithium in hexane (3.9 mL, 0.0089 mol, 2.3 M) was added over 30 min. The resulting solution was stirred an additional 30 min at 0 °C and then cooled to −78 °C. This was then treated with a solution of **7** (2.0 g, 0.0059 mol) in anhydrous THF (15 mL). The resulting solution was stirred at −78 °C for an additional 40 min and then at 0 °C for 30 min. This was then poured into 25% aqueous NaOH (50 mL). The resulting mixture was then washed with ether (to remove starting aldehyde) and then acidified with ice-cold 6 M HCl. This was then extracted with ethyl acetate, the organic extract was washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Recrystallization from Et_2O–hexane (1:10) provided **20** (1.62 g, 65%): mp 141–143 °C; ^1H NMR ($CDCl_3$) δ 1.3 (d, 6 H), 1.6–1.9 (m, 2 H), 2.4 (m, 2 H), 2.8 (m, 2 H), 3.1 (m, 1 H), 3.3 (d, 2 H), 4.5 (m, 1 H), 7.1–7.3 (m, 9 H) ppm; IR (KBr) 2900, 1599, 1511, 1440, 1376, 1273, 1226, 1159, 842, and 766 cm^{-1}. Anal. ($C_{25}H_{25}N_2O_3F$) H, N; C: calcd, 71.41; found, 70.93.

Addition of Benzyl Alcohol to Compound 16. To a solution of **16** (6 g, 0.0148 mol) in benzyl alcohol (45 mL) at 0 °C was added sodium benzylate in benzyl alcohol (5.9 mL, 0.5 M). The reaction was allowed to warm to room temperature and then stirred for 24 h. The solution was then diluted with methanol and made alkaline (0.02 mol, 3 M NaOH). The resulting aqueous layer was washed with ether, acidified with 2 M HCl, and extracted with ethyl acetate. The organic extracts were washed with water and brine and dried ($MgSO_4$). Filtration and concentration yielded a crude mixture of products (7.8 g) consisting mainly of the benzyl ether dihydroxy acid **19** and a small amount of lactone **17**. This material was dissolved in ethyl acetate (30 mL) and 10% Pd/C (0.5 g) added. This was then hydrogenated at 1 atm of pressure for 2 days. The catalyst was then removed by filtration and the filtrate concentrated. The residue was dissolved in toluene (50 mL) and heated to reflux with azeotropic removal of water. The solution was cooled and the product (**10**) crystallized (3.8 g, 60%). HPLC showed a 8:1 trans:cis mixture of diastereomers.

Addition of Methanol to Compound 16. To a solution of compound **16** (1.1 g, 0.0027 mol) in methanol (25 mL) at room temperature under a nitrogen atmosphere was added sodium methoxide (0.017 g, 0.0003 mol). Reaction was almost instantaneous. TLC showed the formation of two products, the main product was presumably the ring opened methyl ether **21**, the minor product was the lactone **22**. This was then made alkaline with 25% NaOH and concentrated in vacuo. The residue was extracted with hexane and the remaining aqueous solution was acidified (0 °C, 12 N, HCl). The solution was then extracted with ethyl acetate and the organic solution was washed with water and brine and dried ($MgSO_4$). Filtration and concentration yielded crude product (1.1 g). This was dissolved in toluene (100 mL) and heated under reflux with azeotropic removal of water for 4 h. Flash chromatography on silica gel eluting with 40% ethyl acetate–hexane gave 6-[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-methoxy-2*H*-pyran-2-one (**22**) (0.89 g, 75%): mp 86–88 °C; HPLC indicated a 7.4:1 mixture of trans (t_R = 23.9 min):cis (t_R = 21.8 min) diastereomers; ^1H NMR ($CDCl_3$) δ 1.25 (d, 6 H), 1.4–1.9 (m, 4 H), 2.4–2.6 (m, 4 H), 3.0 (m, 1 H), 3.2 (s, 3 H), 3.6 (m, 1 H), 4.3 (m, 1 H), 6.9–7.1 (m, 9 H) ppm; IR (KBr) 2958, 1744, 1595, 1565, 1511, 1439, 1376, 1253, 1224, 1157, 1098, 1071, and 840 cm^{-1}. Anal. ($C_{26}H_{29}FN_2O_3$) C, H, N.

(±)-*cis*-6-[2-[5-(4-Fluorophenyl)-3-(1-methylethyl)-1-phenyl-1*H*-pyrazol-4-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (23). A methanolic solution (25 mL) of **20** (1 g, 0.0024 mol) was hydrogenated at atmospheric pressure and room temperature using 10% Ru/C as catalyst. This was stirred at room temperature for 5 days, filtered, and concentrated to yield 1.3 g of crude material. Flash chromatography on silica gel, eluting with 40% ethyl acetate–hexane provided a first fraction identified as **24** (0.55 g, 51%): mp 92–94 °C; ^1H NMR ($CDCl_3$) δ 1.37 (d, 6 H), 1.5 (m, 4 H), 2.4–2.7 (m, 4 H), 3.1 (m, 1 H), 3.7 (s, 3 H), 3.8 (m, 1 H), 4.2 (m, 1 H), and 7.0–7.2 (m, 9 H) ppm; IR (KBr) 2958, 2867, 1735, 1595, 1562, 1511, 1439, 1325, 1337, 1222, 1159, 1093, 983, and 840 cm^{-1}. Anal. ($C_{26}H_{31}FN_2O_4$) C, H, N.

A second fraction gave material identified as **23** (0.13 g, 13%): mp 145–147 °C; HPLC indicated a 4:1 mixture of cis (t_R = 10.51 min):trans (t_R = 11.41 min) diastereomers; ^1H NMR ($CDCl_3$) δ 1.3 (d, 6 H), 1.4–2.0 (m, 4 H), 2.3–2.9 (m, 4 H), 3.1 (m, 1 H), 4.1 (m, 2 H), and 7.0–7.2 (m, 4 H) ppm. Anal. ($C_{25}H_{27}FN_2O_3$) C, H, N.

The other diastereomer exhibits peaks at δ 4.5 ppm (H6′) and 4.3 ppm (H4′); IR (KBr) 3400, 2950, 1700, 1605, 1511, 1376, and 845 cm^{-1}.

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Supplementary Material Available: Preliminary X-ray crystallographic data for lactone **10** (4 pages). Ordering information is given on any current masthead page.