The solution was washed with saturated $NaHCO_3$ and evaporated to dryness. The residue was purified by chromatography on silica gel ($CHCl_3$-MeOH) to give the title compound (387 mg, 24%) after crystallization from petroleum ether: ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H, Me_2Si), 0.89 (s, 9 H, Me_3C), 3.66, 3.77 (A_2B_2, 4 H, $SiOCH_2CH_2O$), 5.25 (s, 2 H, NCH_2O), 5.27 [dd, J = 10.9, 1.1 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.98 [dd, J = 17.6, 1.1 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.42 (dd, J = 17.6, 10.9 Hz, 1 H, C*H*=CH_2), 7.41 (s, 1 H, 6-H), 9.59 (br, 1 H, NH).

1-[[2-[(*tert*-Butyldimethylsilyl)oxy]ethoxy]methyl]-6-(phenylthio)-5-vinyluracil. Following the general procedure for the preparation of **17–19**, the title compound was prepared from the above compound with diphenyl disulfide as an electrophile: yield 46%; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H, Me_2Si), 0.84 (s, 9 H, Me_3C), 3.63 (s, 4 H, $SiOCH_2CH_2O$), 5.33 [dd, J = 11.8, 2.0 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.61 (s, 2 H, NCH_2O), 6.33 [dd, J = 16.8, 2.0 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.71 (dd, J = 16.8, 11.8 Hz, 1 H, C*H*=CH_2), 7.15–7.30 (m, 5 H, SPh), 10.15 (br, 1 H, NH).

Following method A, **55** was prepared from the above compound.

1-[(2-Hydroxyethoxy)methyl]-6-(phenylthio)-5-vinyluracil (55): yield 41%; mp 100–103 °C (EtOAc–petroleum ether); UV (MeOH) λ_{max} 306 (ϵ 7600), 243 nm (ϵ 14 000); MS m/z 320 (M^+); ^1H NMR (Me_2SO-d_6) δ 3.35–3.52 (m, 4 H, $HOCH_2CH_2O$), 4.62 (t, J = 5.4 Hz, 1 H, OH), 5.22 [dd, J = 11.3, 2.2 Hz, 1 H, CH=C*H*(*Z*)H(*E*)], 5.48 (s, 2 H, NCH_2O), 6.21 [dd, J = 16.4, 2.2 Hz, 1 H, CH=CH(*Z*)*H*(*E*)], 6.63 (dd, J = 16.4, 11.3 Hz, 1 H, C*H*=CH_2), 7.23–7.40 (m, 5 H, SPh), 11.75 (br, 1 H, NH). Anal. ($C_{15}H_{16}N_2O_4S \cdot {}^1/_2H_2O$) C, H, N.

Antiviral Assay Procedures. The anti-HIV assays were based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as previously described.[32] Briefly, MT-4 cells were suspended in culture medium at 2.5×10^5 cells/mL and infected with 1000 $CCID_{50}$ (50% cell culture infective dose) of HIV. Immediately after virus infection, 100 μL of the cell suspension was brought into each well of a flat-bottomed microtiter tray containing various concentrations of the test compounds. After a 4 (Table II) or 5 (Table I) day incubation at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method.[33] Cytotoxicity of the compounds was assessed in parallel with their antiviral activity. It was based on the viability of mock-infected host cells as determined by the MTT method.[33]

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(33) Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309–322.

Inhibitors of Cholesterol Biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1*H*-pyrrol-1-yl)ethyl]-2*H*-pyran-2-one Inhibitors of HMG-CoA Reductase. 2. Effects of Introducing Substituents at Positions Three and Four of the Pyrrole Nucleus

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A series of *trans*-tetrahydro-4-hydroxy-6-[2-(2,3,4,5-substituted-1*H*-pyrrol-1-yl)ethyl]-2*H*-pyran-2-ones and their dihydroxy acids were prepared and tested for their ability to inhibit the enzyme HMG-CoA reductase in vitro. Inhibitory potency was found to increase substantially when substituents were introduced into positions three and four of the pyrrole ring. A systematic exploration of structure–activity relationships at these two positions led to the identification of a compound ((+)-**33**, (+)-(4*R*)-trans-2-(4-fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1*H*-pyrrole-4-carboxamide) with five times the inhibitory potency of the fungal metabolite compactin.

Inhibition of HMG-CoA reductase (HMGR), the rate-limiting enzyme in cholesterol biosynthesis, has proven to be an effective means for lowering total and low-density lipoprotein (LDL) cholesterol in animal models and man.[1,2] The early reports describing the activity of the fungal metabolites compactin (mevastatin)[3] and mevinolin (lovastatin)[4] have been followed by a host of publications describing a large variety of natural[5] and synthetic inhibitors.[6] Previously, we disclosed a series of 1,2,5-trisubstituted-pyrrol-1-ylethylmevalonolactones which were found to be moderately potent inhibitors of HMGR in vitro.[7] By systematically altering the 2 and 5 substituents, maximal potency was obtained with the 2-(4-fluorophenyl)-5-isopropyl analogue (1). On the basis of those results, a molecular-modeling analysis led to the description of a pharmacophore model which characterized the size of the substituents at positions 2 and 5 and the conformation of the side chain. We have now discovered

[†] Department of Chemistry.
[‡] Department of Pharmacology.

(1) Roth, B. D.; Sliskovic, D. R.; Trivedi, B. K. *Ann. Rep. Med. Chem.* **1989**, *24*, 147–56.

(2) Grundy, S. M. *N. Engl. J. Med.* **1988**, *319*, 24–32.

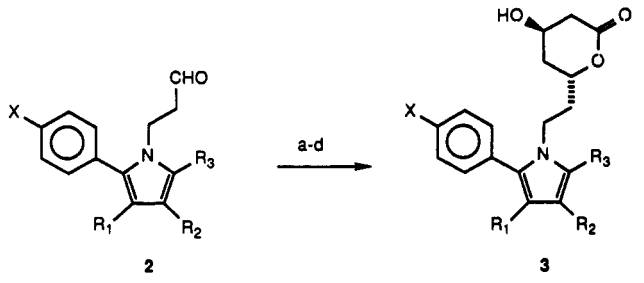
(3) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiotics* **1976**, 1346–8. (b) Endo, A.; Kuroda, Y.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323–6. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–9.

(4) (a) Endo, A. *J. Antibiot.* **1979**, *32*, 852. (b) Alberts, A.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957–61.

(5) Tsujita, Y.; Kuroda, M.; Shimada, Y.; Tanzawa, K.; Arai, M.; Kaneko, I.; Tanaka, M.; Masuda, H.; Tarumi, C.; Watanabe, Y.; Fujii, S. *Biochim. Biophys. Acta.* **1986**, *877*, 50–60.

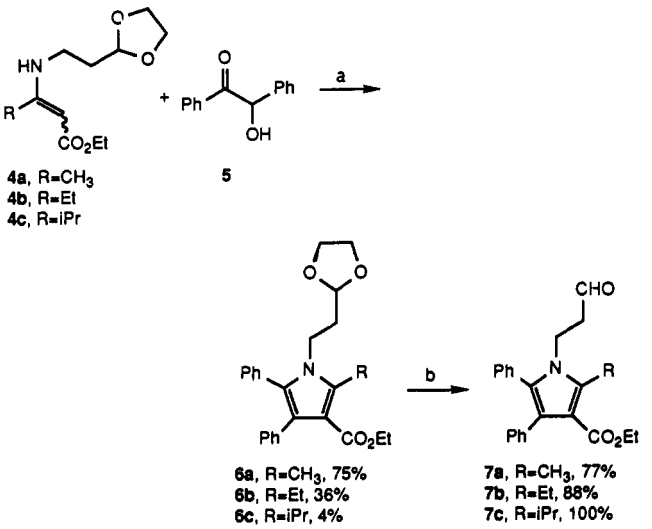
0022-2623/91/1834-0357$02.50/0

Scheme I[a]



[a] (a) $\bar{C}H_2C\bar{O}\bar{C}HCO_2ET$, THF, −78 °C; (b) n-$Bu_3B/NaBH_4$, −78 °C; (c) H_2O_2, NaOH; (d) toluene, reflux.

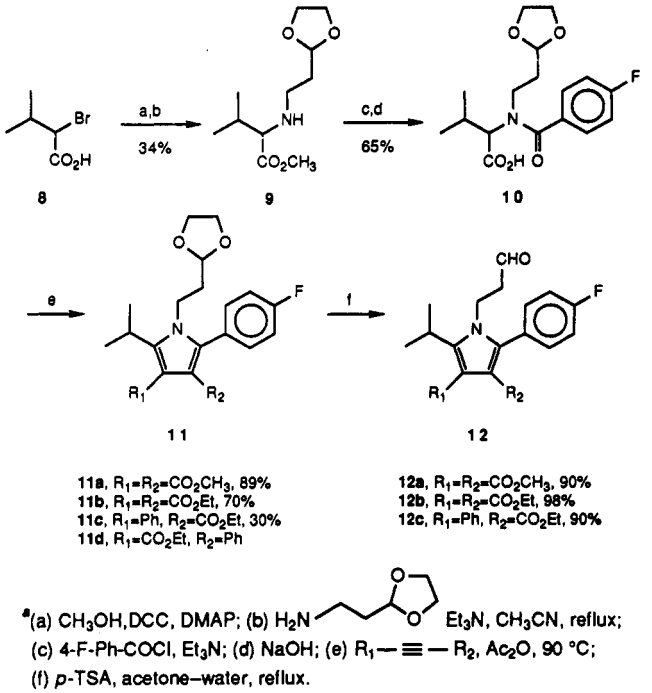
Scheme II. Method A[a]



[a] (a) $ZnCl_2$, EtOH, reflux; (b) p-TSA, acetone–water, reflux.

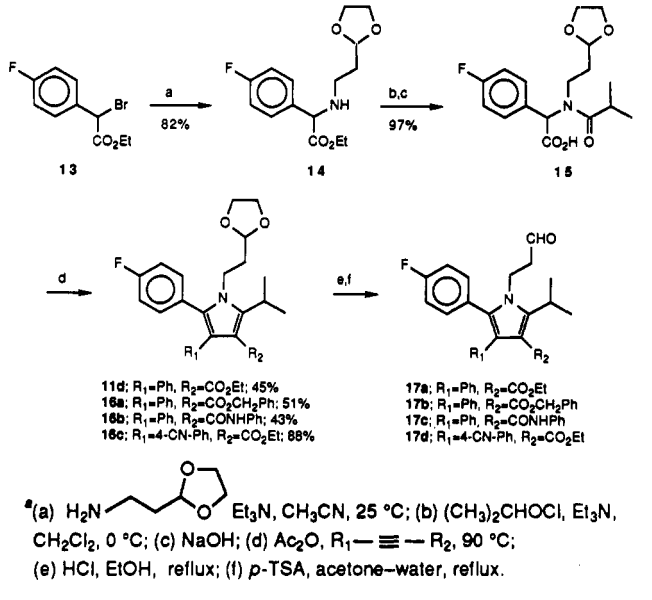
that the introduction of substituents into the 3 and 4 positions of the pyrrole ring results in significant improvements in potency at inhibiting HMGR in vitro. The results of these studies are described in this report.

Scheme III. Method B[a]

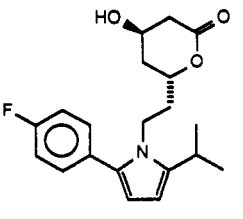


[a] (a) CH_3OH,DCC, DMAP; (b) H_2N Et_3N, CH_3CN, reflux; (c) 4-F-Ph-COCl, Et_3N; (d) NaOH; (e) $R_1-\equiv-R_2$, Ac_2O, 90 °C; (f) p-TSA, acetone–water, reflux.

Scheme IV. Method C[a]



[a] (a) H_2N Et_3N, CH_3CN, 25 °C; (b) $(CH_3)_2CHOCl$, Et_3N, CH_2Cl_2, 0 °C; (c) NaOH; (d) Ac_2O, $R_1-\equiv-R_2$, 90 °C; (e) HCl, EtOH, reflux; (f) p-TSA, acetone–water, reflux.



1

Chemistry

The general synthetic strategy employed was identical with that employed previously.[7] Thus, the pyrrole-3-propionaldehydes **2** were converted to the racemic, trans

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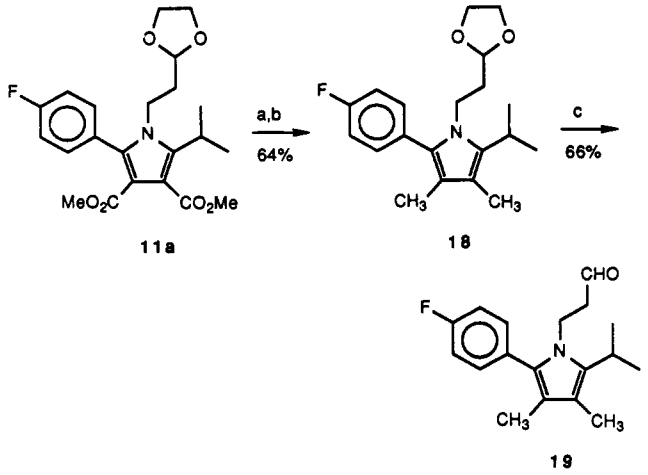
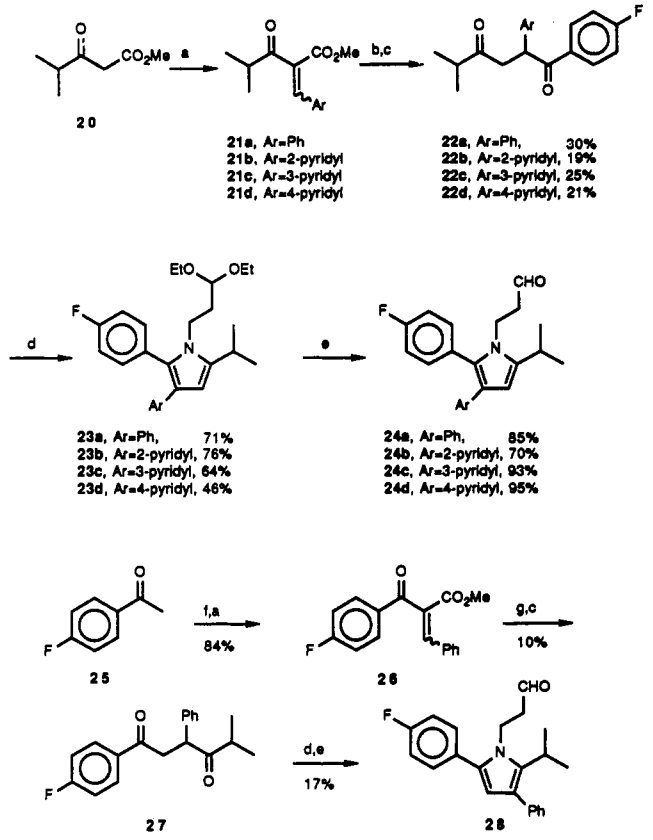
Scheme V. Method D[a]



[a] (a) $LiAlH_4$, ether–dichloromethane, reflux; (b) Et_3SiH, TFA–CH_2Cl_2, 0 °C; (c) *p*-TSA, acetone–water.

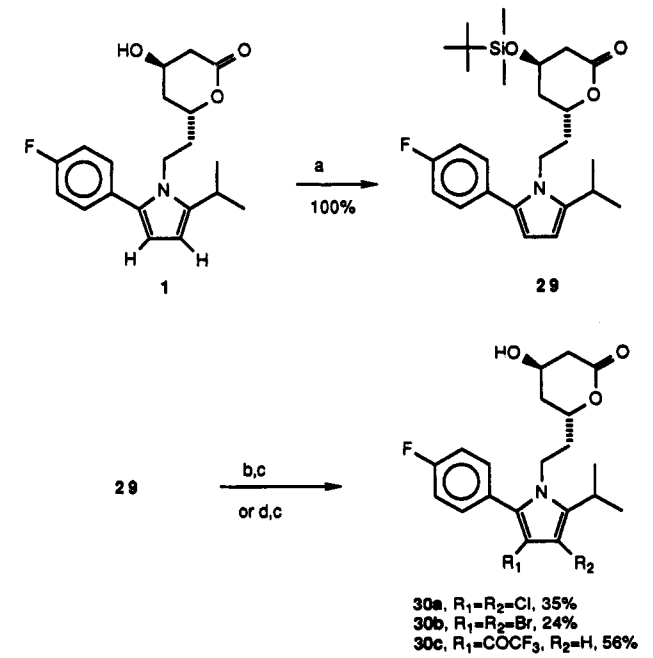
lactone stereoisomers **3** by (1) Weiler dianion condensation with ethyl acetoacetate, (2) stereoselective reduction to the syn-1,3-diol with tributylborane and sodium borohydride, (3) base hydrolysis, and (4) lactonization by refluxing in toluene with azeotropic removal of water (Scheme I). The requisite propionaldehydes **2** were prepared by several different synthetic routes. The less sterically hindered pentasubstituted pyrrole-3-propionaldehydes (**7a**, R = CH_3; **7b**, R = Et, Scheme II) could be prepared by $ZnCl_2$-catalyzed condensation of enamines **4a** and **4b** (prepared from 2-(2-aminoethyl)-1,3-dioxolane[8] and the requisite β-keto ester) with benzoin **5** (method A).[9] This reaction proved ineffective for the more sterically hindered pyrrole **7c**, containing the preferred 5-isopropyl substituent. The 5-isopropylpyrroles could be prepared in good yields, however, by the regioselective [3 + 2] cycloaddition of acetylenes with the amido acids **10** or **15** (Schemes III and IV).[10] Thus, reaction of ethyl phenylpropiolate with amido acid **10** in hot acetic anhydride afforded a 4:1 mixture of **11c** and **11d** (Scheme III, method B) from which **11c** crystallized in 30% yield. The reaction of **15** under identical conditions was regiospecific, producing **11d** as the sole product (Scheme IV, method C). The regiochemistry of compounds **11c** and **11d** were determined by comparison of their proton NMRs with that of the closely related **6c** ($(CH_3)_2CH$, occurs at δ 3.50 ppm in both **6c** and **11d**, but at δ 3.00 ppm in **11c**). As expected, the yield in this cycloaddition reaction was improved when more electron-deficient acetylenes were employed (compare **11a**, **11b**, and **16c** vs **11d** Scheme IV). The 3,4-dimethylpyrrole analogue **19** was prepared by reduction of diester **11a** to the corresponding diol with lithium aluminum hydride, followed by deoxygenation with triethylsilane and trifluoroacetic acid (Scheme V, method D).[11] The regioisomeric 3- and 4-arylpyrrole-3-propionaldehyde isomers **24a–d** and **28** were prepared by a Stetter reaction[12] of the appropriate aldehydes with the complementary α-benzylidene-β-keto esters (4-fluorobenzaldehyde with **21** and isobutyraldehyde with **26**, Scheme VI), followed by Paal–Knorr cyclization[13] with 3,3-diethoxy-1-amino-

Scheme VI. Method E[a]



[a] (a) ArCHO, *p*-TSA, toluene, reflux; (b) 4-F-Ph-CHO, Et_3N, 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride; (c) NaOH, CH_3OH, 25 °C; (d) $H_2NCH_2CH_2CH(OEt)_2$, *p*-TSA, toluene, reflux; (e) H_3O^+, (f) NaH, $(CH_3O)_2CO$; (g) $(CH_3)_2CHCHO$, Et_3N, 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride.

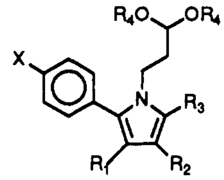
Scheme VII[a]



[a] (a) *t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C, 18 h; (b) 2 equiv *N*-halosuccinimide, DMF, 0 °C; (c) *n*-Bu_4NF, HOAc, THF, 25 °C; (d) $(CF_3CO)_2O$, DMF, 0 °C.

(8) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040–5.
(9) McKinnon, D. M. *Can. J. Chem.* **1965**, *43*, 2628–31.
(10) (a) An extensive review of mesoionic heterocycles has appeared: Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965–3011. (b) An analogous synthesis can be found: Anderson, W. K.; Halat, M. J. *J. Med. Chem.* **1979**, *22*, 977–80.
(11) Doyle, M. P.; DeBruyn, D. J.; Kooistra, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 3659–61.
(12) Stetter, H. *Ang. Chem., Int. Ed. Engl.* **1976**, *15*, 639–47.

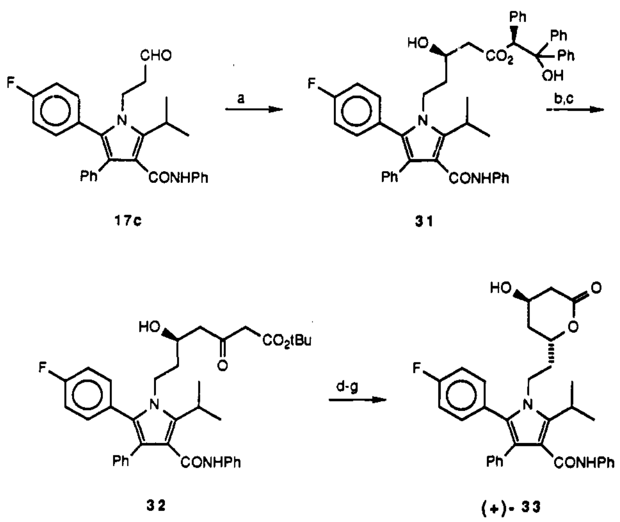
Table I

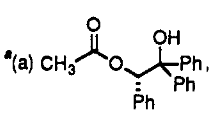
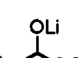


no.	X	R_1	R_2	R_3	R_4	% yield (method)	mp,[a,b] °C
6a	H	Ph	CO_2Et	CH_3	$-CH_2CH_2-$	75 (A)	oil[c]
6b	H	Ph	CO_2Et	Et	$-CH_2CH_2-$	36 (A)	oil[c]
6c	H	Ph	CO_2Et	*i*-Pr	$-CH_2CH_2-$	4 (A)	oil[c]
11a	F	CO_2CH_3	CO_2CH_3	*i*-Pr	$-CH_2CH_2-$	65 (B)	143-6
11b	F	CO_2Et	CO_2Et	*i*-Pr	$-CH_2CH_2-$	70 (B)	oil[c]
11c	F	CO_2Et	Ph	*i*-Pr	$-CH_2CH_2-$	30 (B)	146-8
16a	F	Ph	CO_2Et	*i*-Pr	$-CH_2CH_2-$	45 (C)	158-9
16b	F	Ph	CO_2CH_2Ph	*i*-Pr	$-CH_2CH_2-$	51 (C)	oil[c]
16c	F	Ph	CONHPh	*i*-Pr	$-CH_2CH_2-$	43 (C)	161-3
16d	F	4-CNPh	CO_2Et	*i*-Pr	$-CH_2CH_2-$	88 (C)	oil[c]
18	F	CH_3	CH_3	*i*-Pr	$-CH_2CH_2-$	64 (D)	oil[c]
23a	F	Ph	H	*i*-Pr	Et	71 (E)	84-7
23b	F	2-pyridyl	H	*i*-Pr	Et	76 (E)	84-6
23c	F	3-pyridyl	H	*i*-Pr	Et	64 (E)	96-8
23d	F	4-pyridyl	H	*i*-Pr	Et	46 (E)	123-5

[a] All compounds possess ^1H NMR spectra consistent with assigned structure. [b] Combustion analyses within ±0.4% of theoretical unless otherwise noted. [c] This compound was purified, but not analyzed before use in the next step.

Scheme VIII[a]

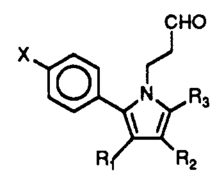


[a] (a)  2LDA, $MgBr_2$, −78 °C; (b) $NaOCH_3$; (c)  (d) Et_3B, NaBH; (e) H_2O_2, CH_3OH; (f) NaOH; (g) $PhCH_3$, reflux.

propane[14] and deprotection (Scheme VI, method E). Finally, the 3,4-dichloro, 3,4-dibromo, and 3-trifluoroacetyl analogues (**30a–c**) were prepared from **1** by protection of the 4′-hydroxyl as the *tert*-butyldimethylsilyl ether, followed by electrophilic substitution on the pyrrole ring[15] and deprotection with n-Bu_4NF buffered with acetic acid (Scheme VII). The assignment of the regiochemistry of **30c** was made in a manner analogous to **11c** and **11d**.

Chiral lactone (+)-**33** was prepared by application of the asymmetric aldol procedure developed by Braun (Scheme VIII).[16] Thus, reaction of aldehyde **17c** with the magnesium enolate of (*S*)-(+)-2-acetoxy-1,1,2-triphenylethanol afforded alcohol **31** in 60% yield and 97% ee. Transesterification ($NaOCH_3$, CH_3OH) followed by Claisen condensation with excess lithio *tert*-butylacetate produced δ-hydroxy-β-keto ester **32** in 75% yield. After reduction with Et_3B and $NaBH_4$, base hydrolysis, and lactonization, (+)-**33** was isolated as a 98:2 mixture of stereoisomers. Fortuitously, the *d,l* pair selectively crystallized from ethyl acetate–hexanes and pure (+)-**33** ($[\alpha]^{23}_D$ = +24.53°, 0.53% in $CHCl_3$) could then be isolated from the mother liquors as a foamy solid.[17]

Table II



no.	X	R_1	R_2	R_3	% yield	mp,[a,b] °C
7a	H	Ph	CO_2Et	CH_3	77	100-1
7b	H	Ph	CO_2Et	Et	88	oil[c]
7c	H	Ph	CO_2Et	*i*-Pr	100	oil[c]
12a	F	CO_2CH_3	CO_2CH_3	*i*-Pr	90	oil[c]
12b	F	CO_2Et	CO_2Et	*i*-Pr	95	oil[c]
12c	F	CO_2Et	Ph	*i*-Pr	90	oil[c]
17a	F	Ph	CO_2Et	*i*-Pr	81	127-8
17b	F	Ph	CO_2CH_2Ph	*i*-Pr	60	oil[c]
17c	F	Ph	CONHPh	*i*-Pr	86	164-5
17d	F	4-CNPh	CO_2Et	*i*-Pr	75	oil[c]
19	F	CH_3	CH_3	*i*-Pr	66	oil[c]
24a	F	Ph	H	*i*-Pr	85	oil[c]
24b	F	2-pyridyl	H	*i*-Pr	70	120-2
24c	F	3-pyridyl	H	*i*-Pr	93	oil[c]
24d	F	4-pyridyl	H	*i*-Pr	95	oil[c]
28	F	H	Ph	*i*-Pr	90	oil[c]

[a] All compounds possessed ^1H NMR and IR spectra consistent with assigned structure. [b] Combustion analyes within ±0.4% of theoretical unless otherwise noted. [c] This compound was purified by chromatography, but not analyzed before use in the next step.

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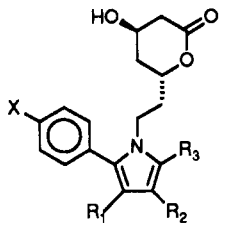
Table III



no.	X	R_1	R_2	R_3	mp, °C	formula[a]	IC_{50},[b] μM	relative potency[c]
1	F	H	H	*i*-Pr	105–6	$C_{20}H_{24}FNO_3$	0.23	10.9
3a	H	Ph	CO_2Et	CH_3	oil	$C_{27}H_{29}NO_5$	4.0	0.6
3b	H	Ph	CO_2Et	Et	65–8	$C_{28}H_{31}NO_5$	0.89	6.3
3c	H	Ph	CO_2Et	*i*-Pr	157–9	$C_{29}H_{33}NO_5$	0.17	23.5
3d	F	CO_2CH_3	CO_2CH_3	*i*-Pr	169–170	$C_{24}H_{28}FNO_7$	0.180	14.3
3e	F	CO_2Et	CO_2Et	*i*-Pr	121–3	$C_{26}H_{32}FNO_7$	0.35	2.8
3f	F	CO_2Et	Ph	*i*-Pr	158–9	$C_{29}H_{32}FNO_5$	0.050	100
3g	F	Ph	CO_2Et	*i*-Pr	159–160	$C_{29}H_{32}FNO_5$	0.20	35.5
3h	F	Ph	CO_2CH_2Ph	*i*-Pr	174–5	$C_{34}H_{34}FNO_5$	0.040	24.0
(±)-**3i**	F	Ph	CONHPh	*i*-Pr	104–110	$C_{33}H_{33}FN_2O_4$	0.025	81.4
3j	F	4-CN-Ph	CO_2Et	*i*-Pr	oil	$C_{30}H_{31}FN_2O_5$	0.280	16.2
3k	F	CH_3	CH_3	*i*-Pr	oil	$C_{24}H_{28}FNO_3$	0.140	16.0
3l	F	Ph	H	*i*-Pr	oil	$C_{26}H_{28}FNO_3$	0.347	12.5
3m	F	2-pyridyl	H	*i*-Pr	186–7	$C_{25}H_{27}FN_2O_3$	0.046	76
3n	F	3-pyridyl	H	*i*-Pr	70–4	$C_{25}H_{27}FN_2O_3$	0.071	9.4
3o	F	4-pyridyl	H	*i*-Pr	174–6	$C_{25}H_{27}FN_2O_3$	0.310	2.1
3p	F	H	Ph	*i*-Pr	135–6	$C_{26}H_{28}FNO_3$	0.120	36.3
30a	F	Cl	Cl	*i*-Pr	129–131	$C_{20}H_{22}Cl_2FNO_3$	0.028	78.6
30b	F	Br	Br	*i*-Pr	141.2	$C_{20}H_{22}Br_2FNO_3$	0.028	78.6
30c	F	$COCF_3$	H	*i*-Pr	oil	$C_{22}H_{23}F_4NO_4$	0.800	8.8
(+)-**33**	F	Ph	CONHPh	*i*-Pr	foam	$C_{33}H_{33}FN_2O_4$	0.007	500
(−)-**33**	F	Ph	CONHPh	*i*-Pr	foam	$C_{33}H_{33}FN_2O_4$	0.440	13.9
		compactin					0.030	100

[a] Analytical results are within ±0.4% of theoretical values except where otherwise noted. [b] CoA reductase inhibition (COR) screen; a measure of the direct conversion of D,L-[^{14}C]HMG-CoA to mevalonic acid. Assays of each inhibitor were performed at four concentrations in triplicate. The precision for compactin was 37%. See ref 7 for experimental details. [c] Calculated as follows: (IC_{50} of compactin/IC_{50} of test compound determined simultaneously) × 100. Compactin arbitrarily assigned a value of 100.

Alternatively, relatively pure (+)- and (−)-**33** could be obtained by preparation of the corresponding diastereomeric (*R*)-α-methylbenzylamides, separation by preparative HPLC, hydrolysis, and relactonization.[6b] This process afforded 94.6% pure (+)-**33** ($[\alpha]^{23}_D$ = +25.5°, 0.51% in $CHCl_3$) and 97.8% pure (−)-**33** ($[\alpha]^{23}_D$ = −24.8°, 0.51% in $CHCl_3$).

Biological Results and Discussion

The compounds listed in Table III were all hydrolyzed to the corresponding dihydroxy acid sodium salts and evaluated for their ability to inhibit a partially purified preparation of rat liver HMG-CoA reductase.[3] Two conclusions were readily apparent. The first was the confirmation of the 5-isopropyl as the preferred substituent (compare **3c** with **3a** and **3b**). The second was the significant increase in in vitro potency found with the introduction of certain lipophilic electron-withdrawing groups into the 3 and 4 positions of the pyrrole ring (e.g., Cl or Br, compare **1** with **30a** and **30b**), such that, these compounds displayed potency equivalent to compactin. This effect did not hold for the esters or ketones (CO_2Me, CO_2Et, $COCF_3$, compounds **3d**, **3e**, **30c**), except when combined with a phenyl (compounds **3f**, **3h**, and **3i**). There also appeared to be a positional effect, since the 3-carbethoxy-4-phenyl analogue (**3f**) was 4 times more potent than the 3-phenyl-4-carbethoxy analogue (**3g**). In vitro activity for the 3-phenyl analogues were improved significantly by increasing the size of the 4-substituent (compare **3h**, **3i**, and **3g** with **3l**). Potency was also increased when the 3-phenyl was replaced with a 3-(2-pyridyl) moiety (compound **3m**). The 3-(3- and 4-pyridyl) isomers (**3n** and **3o**) were equipotent to phenyl (**3l**). Introduction of the electron-withdrawing cyano group into the 4-position of the 3-phenyl (**3j**) led to a slight reduction in potency. Finally, as others have reported, in the case of **3i** essentially all of the biological activity was contained in the dextrorotatory stereoisomer ((+)-**33** vs **3i**).[6b] We speculate that the activity found in (−)-**33** (97.8% pure) is derived from the 2% contamination with (+)-**33**.

An attempt was made to confirm these observations with a quantitative structure–reactivity relationship (QSAR) analysis. In the early stages of the development of the series, there was an indication that size, as parameterized by MR of the combined 3- and 4-substituents, as well as electronic-withdrawing character might be possible contributors to activity and this preliminary analysis partially guided further synthesis. Synthetic constraints precluded the preparation of an optimally designed set, however, and the set of compounds described in this paper did not ultimately support the derivation of a significant Hansch equation including these parameters. Furthermore, available parameters for electronic and lipophilic effects of these highly hindered functional groups are likely to be seriously inaccurate. Nevertheless, the trends observed from plots and single parameter correlations supported the observation that a size benefit exists, but derives mainly from the 4-substituent, as opposed to the 3-substituent. Polar functionality can be tolerated in this region, although there is a suggestion that lipophilicity may ultimately play

(17) A similar sequence was employed by Lynch et al.: Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, 1385–8.

the dominant role among the simple parameterized effects, since $Pi_{3,4}$ has one of the best single parameter correlations with activity ($r = 0.46$). Clearly, other factors not readily parameterized have equal or larger influence on relative activity in this series. The activity of polar-substituted analogues is enhanced when the polar group is "insulated" from the enzyme as in **3m** vs **3n** and **3o**. Similarly, the better activity of **3f** over **3g** may derive from the better shielding of the polar ester group in the former compound by the flanking phenyl groups as opposed to a phenyl and isopropyl group in the latter. The activity of the halogenated analogues **30a** and **30b** is better accommodated by a lipophilicity effect, rather that a size or dispersion effect reflected in MR. Other QSAR analyses of synthetic HMG-CoA reductase inhibitors have reached similar conclusions about structural variations in this region of related molecules.[18,19]

In conclusion, although it is still most critical in this type to have the optimal substituents flanking the dihydroxyglutarate side chain, i.e., 4-fluorophenyl and isopropyl,[7] this work shows that further modulation and improvement in potency at inhibiting HMG-CoA reductase may be obtained with a variety of additional substituents capable of interacting with an apparently fairly spacious hydrophobic region distal from the side-chain location. The importance of this interaction is further supported by the potent inhibition evidenced by other inhibitors which possess substituents in this region.[1] Preparation of the optically pure *R,R*-isomer ((+)-**33**) of the most potent compound in this series (**3i**) resulted in a compound which was 5 times more potent than the fungal metabolite compactin in vitro. Further in vivo studies with (+)-**33** will be described in subsequent papers from this laboratory.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. THF was distilled from sodium and benzophenone. All organic extracts were dried over $MgSO_4$ except when otherwise noted. 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. NMR spectra were determined on either a Varian EM-390 spectrometer, or a Varian XL-200 or Bruker 250 MHz instrument. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. Elemental analyses for carbon, hydrogen, and nitrogen were determined on a Perkin-Elmer Model 240C elemental analyzer and are within 0.4% of theory unless noted otherwise. Optical rotations were determined with use of a Perkin-Elmer 241 polarimeter. Routine HPLC analyses were performed with use of a Varian 5500 unit equipped with a Reodyne 7126 loop injector, a Dupont variable wavelength detector, and an octadecylsilane (Alltech C18 600RP, CH_3CN-H_2O eluant, 60:40, v/v) or silica gel column (Beckman Altex Ultrasphere 5 μm) interfaced to Varian 402 data system for computation of peak areas. Chiral HPLC analyses were performed with use of a Chiracel of 10-μm column (Diacel Chem. Ind., LTD).

Method A. Ethyl 3-[2-(1,3-Dioxolan-2-yl)ethyl]amino-2-pentenoate (4b). A solution of methyl propionylacetate (12.55 mL, 100 mmol), 2-(2-aminoethyl)-1,3-dioxolane[8] (12.3 g, 105 mmol) and one drop of glacial acetic acid was stirred and heated in refluxing toluene (200 mL) for 2 h with azeotropic removal of water. The cooled solution was concentrated to provide 24 g of pure **4b**, which was used without further purification.

Ethyl 2-Ethyl-1-[2-(1,3-dioxolan-2-yl)ethyl]-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (6b). A mixture of benzoin (4.25 g, 20 mmol), **4b** (5.44 g, 22 mmol), and $ZnCl_2$ (6 g, 44 mmol) in 50 mL of absolute ethanol was stirred and heated at reflux for 48 h. The cooled solution was diluted with ether (500 mL), washed with water (50 mL), 2 *M* HCl (2 × 50 mL), saturated aqueous bicarbonate (50 mL), and brine (50 mL), and dried. Flash chromatography (silica gel, 10:1 v/v hexane–ethyl acetate) provided 3 g (36%) of **6b**: 90-MHz NMR ($CDCl_3$) δ 0.98 (t, 3 H, J = 7 Hz), 1.34 (t, 3 H, J = 7 Hz), 1.85 (m, 2 H), 3.08 (q, 2 H, J = 7 Hz), 3.7–4.1 (m, 8 H), 4.60 (t, 1 H, J = 4 Hz), 7.1 (s, 5 H), 7.22 (s, 5 H) ppm.

Ethyl 2-Ethyl-1-[1-(3-oxopropyl)]-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7b). A solution of **6b** (2.4 g, 5.7 mmol) in 100 mL of absolute ethanol containing 1 drop of concentrated HCl was stirred and heated at reflux for 24 h. The cooled solution was concentrated and dissolved in 125 mL of 4:1 acetone–water, and 1 g of *p*-TSA–H_2O was added. The resulting solution was stirred and heated at reflux for 24 h. The cooled solution was concentrated and partitioned between ether and water. The ether layer was then washed with saturated aqueous bicarbonate and brine and dried. Filtration and concentration afforded 1.9 g of **7b** (88%): 90-MHz NMR ($CDCl_3$) δ 1.0 (t, 3 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), 2.58 (m, 2 H), 3.10 (q 2 H, J = 7 Hz), 4.05 (q, 2 H, J = 7 Hz), 4.2 (m, 2 H), 7.05 (s, 5 H), 7.1–7.4 (m, 5 H), 9.50 (s, 1 H) ppm.

Ethyl 3-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-methyl-2-pentanoate (4c). A solution of ethyl isobutyrylacetate (6 g, 42 mmol) and 2-(2-aminoethyl)-1,3-dioxolane (5.4 g, 46.7 mmol) in toluene (50 mL) containing 2 drops of glacial acetic acid was stirred and heated at reflux with azeotropic removal of water for 2 h. Concentration provided crude **4c** which was used without further purification.

Ethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(1-methylethyl)-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (6c). A mixture of **4c** (17 g, 80 mmol), benzoin acetate (75 mmol, 19 g), and $ZnCl_2$ (20 g, 147 mmol) in 100 mL of ethanol was stirred and heated at reflux for 2 days. The mixture was cooled to room temperature, poured into ether (1 L), washed with water (200 mL), 2 M HCl (100 mL), H_2O (100 mL), and brine, and dried. Flash chromatography (silica gel, 10:1 v/v hexane–ethyl acetate) provided 1.2 g of **6c**: 90-MHz NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.45 (d, 6 H, J = 7 Hz), 1.90 (m, 2 H), 3.45 (septet, 1 H, J = 7 Hz), 3.8–4.1 (m, 8 H), 4.60 (t, 1 H, J = 4 Hz), 7.0 (s, 5 H), 7.0–7.3 (m, 5 H) ppm.

Ethyl 1-(3-Oxopropyl)-5-(1-methylethyl)-4,5-diphenyl-1*H*-pyrrole-3-carboxylate (7c). A solution of **6c** (1.3 g, 3 mmol) and *p*-TSA–H_2O (0.6 g, 3 mmol) in 50 mL of 4:1 acetone–water was stirred and heated at reflux overnight. The cooled mixture was poured into ether (200 mL), washed with saturated aqueous bicarbonate (2 × 50 mL), water (50 mL), and brine (50 mL), and dried. Filtration and concentration provided 1.0 g (100%) of pure **7c** which was used without further purification: 90-MHz NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.40 (d, 6 H, J = 7 Hz), 2.55 (m, 2 H), 3.44 (septet, 1 H, J = 7 Hz), 3.95 (q, 2 H, J = 7 Hz), 4.15 (m, 2 H), 7.0 (s, 5 H), 7–7.3 (m, 5 H), 9.43 (s, 1 H) ppm.

Method B. *N*-[2-(1,3-Dioxolan-2-yl)ethyl]-DL-valine, Methyl Ester (9). A solution of the methyl 2-bromo-3-methylbutyrate (4.6 g, 23.6 mmol), 2-(2-aminoethyl)-1,3-dioxolane (2.9 g, 25 mmol), and triethylamine (3.5 mL, 25 mmol) in 25 mL of acetonitrile was stirred and heated at reflux for 20 h. The cooled solution was poured into ether (500 mL) and extracted with 2 M HCl (2 × 50 mL). The aqueous layer was made alkaline with 25% aqueous NaOH and extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate extracts were washed with brine and dried. Filtration and concentration provided 3 g (55%) of **9** as a yellow oil: 90-MHz NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 6H), 1.70 (br s, 1 H, 4NH), 1.86 (m, 2 H), 2.60 (m, 3 H), 2.94 (d, J = 6 Hz, 1 H), 3.68 (s, 3 H), 3.85 (m, 4 H), 4.89 (t, J = 4 Hz, 1 H) ppm.

***N*-[2-(1,3-Dioxolan-2-yl)ethyl]-*N*-(4-fluorobenzoyl)-DL-valine (10).** To a stirred solution of **9** (3 g, 13 mmol) and triethylamine (3.6 mL, 26 mmol) in 20 mL of CH_2Cl_2, cooled to 0 °C, was added a solution of 4-fluorobenzoyl chloride (1.65 mL, 14 mmol) in 10 mL of CH_2Cl_2. The solution was stirred 50 min at 0 °C and 60 min at room temperature. It was then poured into ether (200 mL), washed with water (2 × 50 mL), saturated aqueous bicarbonate (50 mL), and brine (50 mL), and dried. Flash chromatography (silica gel, 1:1 v/v hexane–ethyl acetate) provided 3 g (65%) of crude (±)-methyl *N*-(4-fluorobenzoyl)-*N*-[2-(2-ethyl)-1,3-dioxolanyl]valine: 90-MHz NMR ($CDCl_3$) δ 0.90, (br

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d, J = 7 Hz, 6 H), 1.8–2.5 (m, 3 H), 3.45 (br dd, J = 6, 8 Hz, 1 H), 3.72 (s, 3 H), 3.80 (m, 6 H), 4.80 (m, 1 H), 6.9–7.5 (m, 4 H) ppm.

A solution of this methyl ester (1 g, 2.83 mmol) and NaOH (0.4 g, 10 mmol) in 10 mL of 4:1 methanol–water was stirred and heated at reflux for 3 h. The cooled solution was diluted with water and extracted with ether. The aqueous layer was acidified with 6 M HCl and extracted with ethyl acetate (2×). The combined ethyl acetate extracts were washed with brine and dried. Filtration and concentration provided 0.96 g (2.8 mmol) of **10** as a gum: 90-MHz NMR ($CDCl_3$) δ 0.85 (m, 6 H), 1.8 (m, 2 H), 2.5 (m, 1 H), 3.3–3.9 (m, 7 H), 4.6 (m, 1 H), 6.8–7.4 (m, 4 H) ppm.

Dimethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrole-3,4-dicarboxylate (11a). Dimethyl acetylenedicarboxylate (1.3 mL, 10.6 mmol) was added to a solution of **10** (1.8 g, 5.28 mmol) in 10 mL of acetic anhydride at room temperature. Carbon dioxide evolution began immediately. The solution was stirred a further 2 h, concentrated to remove excess dimethyl acetylenedicarboxylate and solvent, and then filtered through silica gel. This provided 2 g (89%) of **11a** as a colorless solid. Recrystallization from isopropyl ether–hexane afforded colorless crystals: mp 143–146 °C; IR (KBr) 1719, 1449, 1241, 1209, 1178, 945 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 6 H), 1.80 (m, 2 H), 3.18 (septet, J = 7 Hz, 1 H), 3.56 (s, 3 H), 3.7 to 4.0 (m, 6 H), 3.83 (s, 3 H), 4.64 (t, J = 4 Hz, 1 H), 7–7.3 (m, 4 H) ppm. Anal. C, H, N.

Dimethyl 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-(3-oxopropyl)-1*H*-pyrrole-3,4-dicarboxylate (12a). A solution of **11a** (0.5 g, 1.18 mmol) and *p*-TSA–H_2O (0.23 g, 1.2 mmol) in 12 mL of 5:1 acetone–water was stirred and heated at reflux for 48 h. The cooled solution was concentrated, diluted with ether (200 mL), washed with saturated aqueous bicarbonate (2 × 50 mL) and brine (50 mL), and dried. Flash chromatography on silica gel (4:1 v/v hexane–ethyl acetate) provided 0.4 g (90%) of pure **12a**: 90-MHz NMR ($CDCl_3$) δ 1.35 (d, J = 7 Hz, 6 H), 2.61 (t, J = 7 Hz, 2 H), 3.18 (septet, J = 7 Hz, 1 H), 3.53 (s, 3 H), 3.81 (s, 3 H), 4.03 (t, J = 7 Hz, 2 H), 6.9–7.3 (m, 4 H), 9.45 (s, 1 H) ppm.

Ethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-5-(1-methylethyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (11c). A mixture of **10** (3.0 g, 8.8 mmol), acetic anhydride (15 mL), and ethyl phenylpropiolate (3.0 g, 17.6 mmol) was stirred at 110 °C for 5 h. The solution was then cooled and the excess acetic anhydride removed under vacuum. The residual dark oil was purified by flash chromatography on silica gel (4:1 v/v ethyl acetate–hexane). The product solidified on standing and was recrystallized from ether–hexane. The first crop gave 2.2 g (30%) of pure **11c**: 90-MHz NMR ($CDCl_3$) δ 0.65 (t, 3 H, J = 7 Hz), 1.10 (d, 6 H, J = 7 Hz), 1.7–2.0 (m, 2 H), 3.00 (septet, 1 H, J = 7 Hz), 3.6–4.0 (m, 8 H), 4.60 (t, 1 H, J = 4 Hz), 6.9–7.4 (m, 9 H) ppm.

Method C. Ethyl α-[[2-(1,3-Dioxolan-2-yl)ethyl]amino]-4-fluorobenzeneacetate (14). A solution of 26 g (220 mmol) of 2-(2-aminoethyl)-1,3-dioxolane in 50 mL of acetonitrile was added at room temperature with stirring to a solution of 52 g (200 mmol) of ethyl α-bromo-4-fluorobenzeneacetate[20] and 42 mL (300 mmol) of triethylamine in 350 mL of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into ether (500 mL). The suspension which resulted was washed with water (300 mL) and 2 M HCl (2 × 300 mL). The combined acidic extracts were made alkaline with 25% aqueous NaOH and extracted with ethyl acetate (2 × 500 mL). The ethyl acetate extracts were combined, washed successively with water and brine, and dried. Filtration and concentration yielded 49.5 g (82.5%) of **14** as an oil: 90-MHz NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7 Hz), 1.85 (m, 2 H), 2.20 (br s, 1 H), 2.6 (m, 2 H), 3.85 (m, 4 H), 4.1 (q, 2 H, J = 7 Hz), 4.22 (s, 1 H), 4.83 (t, 1 H, J = 4.5 Hz), 6.8–7.3 (m, 4 H) ppm.

α-[[2-(1,3-Dioxolan-2-yl)ethyl](2-methyl-1-oxopropyl)-amino]-4-fluorobenzeneacetic Acid (15). **14** (30 g, 100 mmol) was dissolved in 200 mL of CH_2Cl_2 with 28.6 mL (205 mmol) of triethylamine. The resulting mixture was cooled to 0 °C under dry nitrogen. A solution of 11 mL (105 mmol) of isobutyryl chloride in 50 mL of CH_2Cl_2 was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 1 h and then poured into 100 mL of ether. The ether solution was washed successively with water (25 mL), 2 M HCl (25 mL), saturated aqueous bicarbonate (25 mL), and brine (25 mL), and dried. Filtration and evaporation of the solvents yielded 35 g of α-[[2-(1,3-dioxolan-2-yl)ethyl](2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester: 90-MHz NMR ($CDCl_3$) δ 1.2 (m, 9 H), 1.7 (m, 2 H), 2.85 (m, 1 H), 3.35 (m, 2 H), 3.80 (m, 4 H), 4.20 (q, 2 H, J = 7 Hz), 4.60 (t, 1 H, J = 4.5 Hz), 5.81 (s, 1 H), 6.8–7.3 (m, 4 H) ppm.

A solution of this ester (35 g) and 12 g (300 mmol) of NaOH in 480 mL of 5:1 methanol–water was stirred and heated at reflux for 2 h. The solution was cooled to room temperature, concentrated, and diluted with 500 mL of water. The resulting solution was extracted with ether. The aqueous layer was then acidified with ice-cold 6 M HCl and extracted with ethyl acetate (2 × 300 mL).

The combined ethyl acetate extracts were washed with brine, dried, filtered, and evaporated to yield 30 g of crude **15** as a gum which was used without further purification: 90-MHz NMR ($CDCl_3$) δ 1.11 (d, 6 H, J = 7 Hz), 1.4–1.9 (m, 2 H), 2.85 (m, 1 H), 3.32 (m, 2 H), 3.75 (m, 4 H), 4.52 (t, 1 H, J = 4.5 Hz), 5.73 (s, 1 H), 6.8–7.3 (m, 4 H) ppm.

1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (16b). A solution of 95 g (280 mmol) of **15** and 98 g (439 mmol) of *N*,3-diphenylpropynamide[21] in acetic anhydride (200 mL) was heated at 90 °C with stirring for 4 h (vigorous gas evolution). The mixture was then cooled to room temperature, concentrated, and chromatographed twice on silica gel (4:1 v/v hexane–ethyl acetate) to separate the product (R_f = 0.35, 4:1 hexane–ethyl acetate) from the *N*,3-diphenylpropynamide (R_f = 0.5). Recrystallization of the product from isopropyl ether provided 59.5 g (119 mmol) of **16b** as colorless crystals: mp 159–162 °C; 200-MHz NMR ($CDCl_3$) δ 1.54 (d, 6 H, J = 7 Hz), 1.91 (m, 2 H), 3.60 (septet, 1 H, J = 7 Hz), 3.7–4.1 (m, 6 H), 4.74 (t, 1 H, J = 4.3 Hz), 7.0–7.3 (m, 15 H); IR (KBr) 3400, 1658, 1596, 1530 cm^{-1}. Anal. C, H, N.

5-(4-Fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (17c). A solution of 59 g (118 mmol) of **16c** and 0.4 mL of concentrated HCl in 1200 mL of absolute ethanol was heated under reflux with stirring for 24 h. The mixture was cooled to room temperature and concentrated and the residue taken up in 3:1 acetone–water (1200 mL). *p*-TSA–H_2O (5 g) was added. This mixture was heated under reflux with stirring for 2 days, cooled to room temperature, and partitioned between ether (1000 mL) and brine (200 mL). The organic layer was separated, washed successively with saturated aqueous bicarbonate (2 × 200 mL) and brine (100 mL), dried, filtered, and concentrated. The resulting oil was dissolved in the minimum amount of hot isopropyl ether, and the crystals which formed upon cooling were collected by filtration to yield 36.8 g (81 mmol) of **17c**, mp 164–5 °C. A further crop of 9.8 g was obtained from the mother liquor: 200-MHz NMR ($CDCl_3$) δ 1.52 (d, 6 H, J = 7 Hz), 2.68 (br t, 2 H, J = 4 Hz), 3.63 (septet, 1 H, J = 7 Hz), 4.27 (br t, 2 H, J = 4 Hz), 6.86 (br s, 1 H), 7.0–7.2 (m, 14 H), 9.60 (s, 1 H); IR (KBr) 3400, 2966, 1720, 1673, 1596, 1511 cm^{-1}. Anal. C, H, N.

Methyl 7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-5-oxo-1-heptanoate. A solution of methyl acetoacetate (26.4 mL, 243 mmol) in 250 mL of anhydrous THF was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 mL of THF at 0 °C. When gas evolution was complete, 97.2 mL of a 2.5 M solution of *n*-butyllithium in hexanes was added dropwise over 1 h.

The resulting solution was stirred for 30 min at 0 °C and cooled to −78 °C, and a solution of 36.8 g (81 mmol) of **17c** in 100 mL of THF was added over a period of 30 min. The resulting solution was stirred for 30 min at −78 °C, then warmed to 0 °C, and held for an additional 1 h.

(20) Epstein, J. W.; Brabander, H. J.; Fanshawe, W. J.; Hofmann, C. M.; McKenzie, T. C.; Safir, S. R.; Osterberg, A. C.; Cosulich, D. B.; Lovell, F. M. *J. Med. Chem.* **1981**, *24*, 481–90.

(21) Cabre, J.; Palomo, A. L. *Synthesis* **1984**, 413–7.

The mixture was then acidified by the dropwise addition of 300 mL of ice-cold 3 M HCl, diluted with ether, washed with water and brine, dried, filtered, and evaporated. Flash chromatography on silica gel (3:1 v/v hexane–ethyl acetate) yielded 37.9 g of methyl 7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate: 90-MHz NMR ($CDCl_3$) δ 1.50 (d, 6 H, J = 7 Hz), 1.8 (m, 2 H), 2.45 (d, 2 H, J = 7 Hz), 2.8 (br s, 1 H), 3.33 (s, 2 H), 3.5 (m, 1 H), 3.67 (s, 3 H), 3.8–4.0 (m, 2 H), 6.8–7.3 (m, 14 H) ppm.

(±)-*trans*-5-(4-Fluorophenyl)-2-(1-methylethyl)-*N*,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-3-carboxamide (3i). Air (60 mL) was bubbled via a syringe through a solution of methyl 7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate (48 g, 84 mmol) and 92.5 mL of a 1 M THF solution of tributylborane in 100 mL of anhydrous THF. The mixture was stirred overnight at room temperature and then cooled to −78 °C. Sodium borohydride (3.85 g, 102 mmol) was added to the cooled mixture in one portion. The vigorously stirred suspension was allowed to warm slowly to 0 °C over 3 h (vigorous gas evolution ensued).

The dry ice–acetone bath cooling the reaction vessel was replaced by an ice bath and 18.3 mL of glacial acetic acid was added dropwise, followed by 204 mL of 3 N NaOH and 30.5 mL of 30% aqueous H_2O_2.

The mixture was vigorously stirred and allowed to warm to room temperature overnight. The mixture was partitioned between ether and water. The aqueous layer was separated, acidified, and extracted with ethyl acetate (2×).

The ethyl acetate extracts were washed with brine, dried, and evaporated to yield crude (*R**,*R**)-3,5-dihydroxy-7-[(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and heated at reflux for 6 h with azeotropic removal of water. Chromatography (silica gel, 1:1 v/v hexane–ethyl acetate) provided 30 g of **3i** as a foamy solid, mp 90–97 °C.

This material was found by HPLC analysis to be a 9:1 mixture cis and trans isomers. Recrystallization from toluene–ethyl acetate yielded essentially pure trans **3i**: mp 148–9 °C; 200-MHz NMR ($CDCl_3$) δ 1.52 (m, 6 H), 1.6–2.0 (m, 4 H), 2.48 (br s, 1 H), 2.51 (m, 2 H), 3.55 (septet, 1 H, J = 7 Hz), 4.0–4.2 (m, 2 H), 4.29 (m, 1 H), 4.52 (m, 1 H), 6.90 (br s, 1 H), 7.0–7.3 (m, 14 H) ppm; IR (KBr) 3400, 1734, 1654, 1597, 1511 cm^{-1}. Anal. C, H, N.

Phenylmethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-1*H*-pyrrole-3-carboxylate (16a). A solution of **15** (10 g, 29 mmol) and benzyl phenylpropiolate (7.7 g, 44 mmol) was stirred and heated in 30 mL of acetic anhydride at 90 °C for 6 h. After cooling to room temperature, the solution was concentrated, diluted with ether, washed with water, saturated aqueous bicarbonate, and brine, and dried. Flash chromatography on silica gel (10:1 v/v hexane–ethyl acetate) provided 5.9 g (45%) of crude **16a**. Recrystallization from isopropyl ether provided 4.8 g of colorless **16a**: mp 158–9 °C; IR (KBr) 1683 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7 Hz), 1.48 (d, 6 H, J = 7 Hz), 1.93 (m, 2 H), 3.50 (septet, 1 H, J = 7 Hz), 3.7–4.1 (m, 8 H), 4.71 (t, 1 H, J = 4.4 Hz), 6.95–7.2 (m, 9 H) ppm. Anal. C, H, N.

Method D. 1-[2-(1,3-Dioxolan-2-yl)ethyl]-2-(4-fluorophenyl)-3,4-dimethyl-5-(1-methylethyl)-1*H*-pyrrole (18). A solution of **11a** (1.0 g, 2.37 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a stirred suspension of lithium aluminum hydride (0.3 g, 7.4 mmol) in 20 mL of ether at room temperature. When addition was complete, the mixture was heated to reflux for 30 min, cooled to room temperature, and quenched by dropwise addition of water (0.3 mL), 25% aqueous NaOH (0.2 mL), and water (0.9 mL). After stirring vigorously for 30 min, the mixture was filtered and washed well with CH_2Cl_2. The filtrated was dried, filtered, and concentrated, providing 0.78 g (90%) of pure diol.

Trifluoroacetic acid (5.2 mL, 67 mmol) was added to a stirred solution of the diol (1.23 g, 3.4 mmol) and triethylsilane (1.2 mL, 7.5 mmol) in 10 mL of CH_2Cl_2 cooled to 0 °C under dry nitrogen. The solution was stirred for 2 h at 0 °C before warming to room temperature for 1 h. It was then poured into 300 mL of 50:50 ether–hexane and washed with saturated aqueous bicarbonate (3 × 50 mL) and brine (50 mL), and dried. Flash chromatography on silica gel (10:1 v/v hexane–ethyl acetate) provided 0.80 g (71%) of **18** as an oil: 90-MHz NMR ($CDCl_3$) δ 1.32 (d, 6 H, J = 7 Hz), 1.7–1.9 (m, 2 H), 1.86 (s, 3 H), 2.07 (s, 3 H), 3.10 (septet, 1 H, J = 7 Hz), 3.7–4.0 (m, 6 H), 4.58 (t, 1 H, J = 4 Hz), 6.9–7.3 (m, 4 H) ppm.

Method E. Methyl 4-Methyl-3-oxo-2-(phenylmethylene)pentanoate (21a). A mixture of methyl isobutyrylacetate (144 g, 1 mol), benzaldehyde (116 g, 1.1 mol), piperidine (4 mL), and HOAc (12 mL) in 200 mL of toluene was stirred and heated at reflux with azeotropic removal of water for 3 h. The solution was cooled, poured into ether (1 L), washed with 1 M HCl (200 mL), saturated aqueous bicarbonate (200 mL), and brine, and dried. Concentration and distillation (bp 127–130 °C/1 mmHg) provided 186.6 g (80%) of **21a** as a mixture of diastereomers (isomer 1, major ~70%): 90-MHz NMR ($CDCl_3$) δ 0.98 (d, 6 H, J = 7 Hz), 2.58 (septet, 1 H, J = 7 Hz), 3.70 (s, 3 H), 7.28 (s, 5 H), 7.68 (s, 1 H) ppm. Isomer 2: 90-MHz NMR ($CDCl_3$) δ 1.14 (d, 6 H, J = 7 Hz), 3.14 (septet, 1 H, J = 7 Hz), 3.70 (s, 3 H), 7.80 (s, 5 H), 7.48 (s, 1 H) ppm.

1-(4-Fluorophenyl)-5-methyl-2-phenyl-1,4-hexanedione (22a). To a solution of **21a** (376 g, 1.62 mol), 4-fluorobenzaldehyde (201 g, 1.62 mol), and Et_3N (158 mL) in a 3-L three-neck round-bottom flask with an air-driven stirrer was added 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride (65.5 g, 243 mmol). The mixture was stirred and heated at 70 °C for 24 h. After cooling to room temperature, the mixture was diluted with ether (3 L), washed with water, dilute HCl, saturated aqueous bicarbonate, and brine, and dried. The crude oil which remained after filtration and concentration was dissolved in THF (1500 mL) and added to a solution of NaOH (130 g) in 750 mL of water. The mixture was vigorously stirred overnight, acidified (pH 5) with 6 N HCl, and extracted with ether. The ether layer was washed several times with 3 N NaOH and water (to remove a low R_f, base soluble material) and brine and dried. The crude material was filtered through silica gel (100 g) and concentrated. It was then Kugelrohr distilled in two portions to afford 314 g (66%) of **22a**: bp 145 °C (0.3 mmHg) IR (film) 1711, 1684, 1600 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.08 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 2.65 (septet, 1 H, J = 7 Hz), 2.77 (dd, 1 H, J = 18, 4 Hz), 3.63 (dd, 1 H, J = 18, 10 Hz), 5.07 (dd, 1 H, J = 10, 4 Hz), 7.10 (m, 2 H), 7.27 (m, 5 H), 7.98 (m, 2 H) ppm.

1-(3,3-Diethoxypropyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-1*H*-pyrrole (23a). To a solution of **22a** (230 g, 0.77 mol) in 1 L of toluene was added 3,3-diethoxy-1-aminopropane[19] (176 g, 1.2 mol) at room temperature. The mixture solidified, but dissolution occurred on adding *p*-TSA–H_2O and heating to reflux (Dean–Stark) for 24 h. To the cooled solution was added 100 mL of absolute ethanol and the mixture concentrated and filtered through silica gel. The residue on concentration was dissolved in the minimum amount of isopropyl ether and allowed to crystallize. A first crop of 89 g (mp 84–7 °C) was isolated. A further 145 g were isolated as an oil: IR (KBr) 2973, 1603, 1511 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.11 (t, 3 H, J = 7 Hz), 1.35 (d, 6 H, J = 7 Hz), 1.75 (m, 2 H), 3.04 (septet, 1 H, J = 7 Hz), 3.2–3.6 (m, 4 H), 3.91 (m, 2 H), 4.27 (t, 1 H, J = 4.4 Hz), 6.20 (s, 1 H), 7.0–7.4 (m, 9 H) ppm. Anal. C, H, N.

Methyl 3-(4-Fluorophenyl)-3-oxopropanoate. To a suspension of dimethyl carbonate (195 g, 2.17 mmol) and hexane-washed NaH (72g, 3.0 mol) in dry THF (600 mL) at 60 °C was added 164 g (1.2 mol) of *p*-fluoroacetophenone dropwise. The reaction was maintained at gentle reflux by adjusting the temperature and addition rate (exothermic). After the addition was complete, the reaction was heated at reflux for 4 h, then cooled to room temperature.

The reaction was poured carefully into ice cold acetic acid (183 mL, 3.2 mol) and water (400 mL). The product was extracted with ether (2×), and the combined ether layers were washed with saturated aqueous bicarbonate, brine and dried. Distillation provided 204 g (96%) of desired product (bp 91 °C/0.5 mmHg): 90-MHz NMR ($CDCl_3$) δ 3.65 (s, 3 H), 3.92 (s, 2 H), 6.82–7.20 (m, 2 H), 7.57–8.01 (m, 2 H), 12.45 (singlet, 1 H) ppm.

Methyl 3-(4-Fluorophenyl)-3-oxo-2-(phenylmethylene)propanoate (26). A mixture of methyl, 3-(4-fluorophenyl)-3-oxopropionate (100 g, 510 mmol), benzaldehyde (59.5 g, 561 mmol), piperidine (2 mL), and acetic acid (6 mL) in toluene (100 mL)

was stirred and heated at reflux with azeotropic removal of water for 4 h. The solution was cooled and filtered through silica gel (600 g) with toluene as eluant. Concentration afforded 127.2 g (88%) of **26** as a mixture of *E*- and *Z*-isomers: 90-MHz NMR ($CDCl_3$) δ 2.22 (s, 3 H, isomer 1), 3.62 (s, 3 H, isomer 2), 6.80–8.11 (m, 10 H) ppm.

1-(4-Fluorophenyl)-3-phenyl-5-methylhexane-1,4-dione (27). A mixture of **26** (130 g, 454 mmol), isobutyraldehyde (41 mL, 454 mmol), Et_3N (33 mL), and 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride (24 g, 91 mmol) was stirred and heated at 70 °C for 18 h. Additional isobutyraldehyde (6 g) was added and stirring continued for a further 6 h. After cooling to room temperature, the mixture was diluted with ether, washed with 2 M HCl (2×), saturated aqueous bicarbonate, and brine, and dried. The crude product was used without further purification.

To a solution of the crude diketo ester (31 g, 86.9 mmol) in 5:1 THF–H_2O (500 mL) was added NaOH (8 g, 200 mmol) in one portion. A small amount of methanol was added to ensure homogeneity. The reaction was stirred overnight at room temperature. The solvent was removed on the rotary evaporator, and the residue was dissolved in ether. This was then washed with 2 M HCl and brine and dried. Purification by flash chromatography (9:1 v/v ethyl acetate–hexane) gave 9.0 g (35%) of **27** as an oil: 90-MHz NMR ($CDCl_3$) δ 0.8 (d, 3 H, J = 7 Hz), 1.2 (d, 3 H, J = 7 Hz), 2.4–3.0 (m, 1 H), 3.6–4.0 (m, 1 H), 4.4–4.55 (m, 1 H), 6.8–7.3 (m, 7 H), 7.7–7.9 (m, 2 H) ppm.

5-(4-Fluorophenyl)-2-(1-methylethyl)-3-phenyl-1*H*-pyrrole-1-propanal (28). To a solution of **17** (9.0 g, 30.2 mmol) and 3,3-diethoxy-1-aminopropane (6.6 g, 45.3 mmol) in toluene (150 mL) was added a catalytic amount of *p*-TSA–H_2O. The resulting mixture was heated to reflux with azeotropic removal of water (Dean–Stark) overnight.

The solution was cooled and concentrated, and the residue was purified by flash chromatography on silica gel (10:1 v/v ethyl acetate–hexane). This provided 2.4 g (19%) of the pyrrole acetal as an oil and 7.1 g of recovered **27**. The pyrrole acetal was taken up in 5:1 acetone–water. Camphorsulfonic acid (0.2 g) was added and the solution refluxed for 18 h. The cooled solution was concentrated, diluted with ether, washed with water, bicarbonate, and brine, and dried. Flash chromatography on silica gel (9:1 v/v hexane–ethyl acetate) afforded 1.9 g of **28** as an oil: 90-MHz NMR ($CDCl_3$) δ 1.3 (d, 6 H, J = 7 Hz), 2.56 (m, 2 H), 3.22 (septet, 1 H, J = 7 Hz), 4.37 (m, 2 H), 6.1 (s, 1 H), 6.9–7.5 (m, 9 H), 9.5 (s, 1 H) ppm.

(2*R*)-*trans*-4-[[(1,1-Dimethylethyl)silyl]oxy]-6-[2-[2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]ethyl]-tetrahydro-2*H*-pyran-2-one (29). To a solution of **1** (0.52 g, 1.5 mmol) and *tert*-butyldimethylchlorosilane (0.27 g, 1.8 mmol) in 5 mL of dry DMF was added imidazole (0.31 g, 4.5 mmol) in one portion. The solution was stirred overnight at room temperature before partitioning between hexane (100 mL) and water (50 mL). The aqueous layer was extracted with two 50-mL portions of hexane. The combined hexane extracts were washed with water (2 × 25 mL) and brine (25 mL) and dried. Filtration through silica gel and concentration provided 0.7 g (100%) of **29** as a colorless oil: 90-MHz NMR ($CDCl_3$) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.30 (d, J = Hz, 6 H), 1.4–1.8 (m, 4 H), 2.48 (m, 2 H), 2.95 (m, 1 H), 3.9–4.3 (m, 3 H), 5.85 (d, J = 2 Hz, 1 H), 6.02 (d, J = 2 Hz, 1 H), 6.8–7.3 (m, 4 H).

(2*R*)-*trans*-6-[2-[3,4-Dichloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (30a). *N*-Chlorosuccinimide (6.48 mmol, 0.87 g) was added in one portion to a stirred solution of **29** (1.49 g, 3.24 mmol) in dry DMF (10 mL) cooled to 0 °C under dry nitrogen. The solution was stirred for 1 h at 0 °C then warmed to room temperature over 3 h. This was then diluted with water (50 mL) and extracted with ether (2 × 100 mL). The ether extracts were diluted with 100 mL of hexane, washed with water (50 mL), saturated aqueous bicarbonate (50 mL), 10% aqueous $NaHSO_3$ (50 mL), and brine (50 mL), and dried. After filtration and concentration, the crude product was dissolved in THF (15 mL) and treated with glacial acetic acid (0.75 mL, 13 mmol) and n-Bu_4F (9.72 mL of 1 M THF solution). The solution was stirred for 5 h, diluted with ethyl acetate (100 mL), washed with saturated aqueous bicarbonate (2 × 50 mL) and brine (25 mL), and dried. The residue which remained after filtration and concentration was flash chromatographed on silica gel (2:1 v/v hexane–ethyl acetate). This provided 0.50 g (35%) of **30a** as a colorless solid. Recrystallization from ether–hexane provided colorless crystals: mp 129–131 °C; IR (KBr) ν 3550, 2990, 1711, 1518, 1225, 1160, 1055, 851, 816 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.44 (d, J = 7 Hz, 6 H), 1.8 (m, 4 H), 2.12 (d, J = 3 Hz, 1 H, OH), 2.55 (m, 2 H), 3.10 (m, 1 H), 4.0 (m, 2 H), 4.30 (m, 1 H), 4.45 (m, 1 H), 7.0–7.4 (m, 4 H) ppm. Anal. C, H, N.

(2*R*)-*trans*-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(trifluoroacetyl)-1*H*-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2*H*-pyran-2-one (30c). Trifluoroacetic anhydride (0.17 mL, 1.2 mmol) was added dropwise to a stirred solution of **29** (0.50 g, 1.09 mmol) in 2 mL of DMF cooled to 0 °C under nitrogen. The light yellow solution was stirred for 1 h at 0 °C, diluted with 150 mL of 50:50 ether–hexane, washed with saturated aqueous bicarbonate (3 × 50 mL), and brine, and dried. Filtration and concentration provided a single product which was dissolved in 5 mL of anhydrous THF and stirred overnight at room temperature with 4 equiv of glacial acetic acid and 3 equiv of n-Bu_4NF. The mixture was then diluted with ether, washed with 2 M HCl and brine, and dried. Flash chromatography on silica gel (2:1 v/v hexane–ethyl acetate) provided 0.25 g of **30c** as an oil: IR (KBr) 3450, 1687, 1609 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.31 (d, 6 H, J = 7 Hz), 1.4–2.0 (m, 5 H), 2.6 (m, 2 H), 3.00 (septet, 1 H, J = 7 Hz), 3.9–4.1 (m, 2 H), 4.33 (m, 1 H), 4.49 (m, 1 H), 6.48 (q, 1 H, J = 2.1 Hz), 7.0–7.4 (m, 4 H) ppm. Anal. C, H, N.

[*S*-(*R,*S**)]-5-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoic Acid, 2-Hydroxy-1,2,2-triphenylethyl Ester (31).** n-Butyllithium in hexane (285 mL, 2.2 M) was added dropwise with stirring to diisopropylamine (92 mL) in THF (300 mL) at −50 to −60 °C in a 1000-mL one-neck flask via a dropping funnel under nitrogen. The yellow solution was allowed to warm to approximately −20 °C, then cannulated into a suspension of 99 g of (*S*)-(+)-2-acetoxy-1,1,2-triphenylethanol[16] in 500 mL of anhydrous THF at −70 °C. When addition was complete, the reaction mixture was allowed to warm to −10 °C over a period of 2 h. Meanwhile, a suspension of 0.63 mol of $MgBr_2$ was prepared by addition of 564 mL (0.63 mol) of bromine dropwise into a suspension of 15.3 g of magnesium (0.63 mol) in 500 mL of THF in a 3-L flask equipped with reflux condenser and mechanical stirrer. The $MgBr_2$ suspension was cooled to −78 °C and the enolate solution cannulated into the suspension over 30 min. Stirring was continued for 1 h at −78 °C. **17c** (150 g) in 800 mL of THF was then added dropwise over 30 min. The solution was stirred for 1.5 at −78 °C and then quenched with 200 mL of glacial acetic acid at −78 °C. After warming to 0 °C, 500 mL of water were added and the mixture concentrated in vacuo at 40–50 °C. 1:1 ethyl acetate–heptane (500 mL) was added to the yellow slurry, which was then filtered. The filtrate was washed extensively with 0.5 N HCl, then several times with water, and finally with cold (−20 °C) ethyl acetate–heptane (3:1). The light brown crystalline product was dried in vacuo at 40 °C, affording 194 g of crude aldol product. Recrystallization from ethyl acetate at −10 °C yielded 100 g of **31** (mp 229–230 °C) which analyzed as a 97.4:2.2 mixture of the *R,S*-:*S,S*-isomers by HPLC: IR (KBr) 3400, 2961, 1716, 1663, 1595, 1511, 701 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.44 (d, 6 H, J = 7 Hz), 1.5 (m, 2 H), 2.12 (m, 2 H), 2.39 (br s, 1 H) 3.40 (septet, 1 H, J = 7 Hz), 3.62 (m, 1 H), 3.81 (m, 1 H), 4.07 (m, 1 H), 6.63 (s, 1 H), 6.8–7.5 (m, 29 H) ppm. Anal. C, H, N.

Methyl (*R*)-(+)-5-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoate. To a suspension of 162 g (0.206 M) of the triphenylethanediol ester prepared above in 800 mL methanol–THF (5:3) cooled to 0 °C was added 11.7 g of sodium methoxide. The mixture was stirred until dissolution occurred and then put in the freezer overnight. The reaction mixture was then allowed to warm to room temperature, quenched with 15 mL of glacial acetic acid and concentrated in vacuo at 40 °C to obtain an oil, which was partitioned between water (500 mL) and ethyl acetate (2 × 300 mL). The combined organic extracts were washed with saturated aqueous bicarbonate and brine, dried, and filtered and the solvent evaporated. The residue was chromatographed on silica gel (1:4 v/v, ethyl acetate–heptane) to yield 109 g of the methyl ester as a colorless oil which solidified on

standing. Recrystallization from ether–heptane yielded 73.9 g of colorless crystals: mp 125–6 °C; $[\alpha]^{20}_D$ = 4.23° (1.17 M, CH_3OH); IR (KBr) 3400, 2960, 1720, 1646, 1511, 1160, 755 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 1.53 (d, 6 H, J = 7 Hz) 1.6–1.7 (m, 2 H), 2.30 (d, 2 H, J = 6 Hz), 2.88 (br s, 1 H), 3.57 (septet, 1 H, J = 7 Hz), 3.67 (s, 3 H), 3.85 (m, 1 H), 3.97 (m, 1 H), 4.15 (m, 1 H), 6.85 (s, 1 H), 6.95–7.25 (m, 14 H) ppm. Anal. C, H, N.

1,1-Dimethylethyl (*R*)-7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-1-heptanoate (32). Diisopropylamine (75 mL, 550 mmol) was dissolved in THF (250 mL) in a 2000-mL three-neck flask equipped with thermometer and dropping funnel under nitrogen. The mixture was cooled to −42 °C and then 200 mL of 2.2 M *n*-butyllithium in hexane was added dropwise over 20 min. After stirring for 20 min, 62 mL (460 mmol) of *tert*-butyl acetate dissolved in THF (200 mL) was added over 30 min. This mixture was stirred for 30 min at −40 °C, then a further 140 mL of 2.2 M *n*-butyllithium was added over 20 min. When addition was complete, 81 g (153 mmol) of methyl (*R*)-(+)-5-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3-hydroxy-1-pentanoate in anhydrous THF (500 mL) was added as quickly as possible without allowing the temperature to rise above −40 °C. Stirring was continued for 4 h at −70 °C. The reaction mixture was quenched with glacial acetic acid (69 mL) and allowed to warm to room temperature. It was then concentrated in vacuo and the residue taken up in ethyl acetate, washed extensively with water, saturated aqueous NH_4Cl, saturated aqueous bicarbonate, and brine. The organic layer was dried and filtered and the solvent evaporated to produce 73 g of **32**: IR (KBr) 3400, 2933, 1700, 1665, 1511, 1151 cm^{-1}; 200-MHz NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.53 (dd, 6 H, J = 7.1 Hz), 1.6 (m, 2 H), 2.51 (s, 1 H), 2.53 (d, 1 H, J = 2 Hz), 2.80 (d, 1 H, J = 2 Hz, O*H*), 3.31 (s, 2 H), 3.60 (septet, 1 H, J = 7 Hz), 3.9–4.0 (m, 2 H), 4.09–4.22 (m, 1 H), 6.85 (s, 1 H), 6.95–7.2 (m, 14 H) ppm. Anal. C, H, N.

(+)-(4*R*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((+)-33). To a solution of 73 g (119 mmol) of **32** in THF (500 mL) was added triethylborane (120 mL of a 1 M THF solution) and pivalic acid (0.7 g). The mixture was stirred for 10 min and cooled to −78 °C and methanol (70 mL) was added, followed by $NaBH_4$ (4.5 g, 119 mmol). The mixture was stirred at −78 °C for 6 h, then poured slowly into a 4:1:1 mixture of ice–30% aqueous H_2O_2–water. This mixture was stirred overnight and then allowed to warm to room temperature. Chloroform (400 mL) was added and the mixture partitioned between chloroform and water. The aqueous layer was further extracted with chloroform. The organic extracts were combined and washed extensively with water until a test for peroxide was negative. The organic layer was dried, filtered, and evaporated. The residue was flash chromatographed on silica gel (1:3 v/v ethyl acetate–hexane) to yield 51 g of crude dihydroxy ester which was dissolved in THF–methanol and 1 N NaOH (100 mL) was added with stirring at room temperature. After 4 h, the solution was concentrated, water (100 mL) was added, and it was extracted with ether (2 × 100 mL). The aqueous layer was acidified with 1 N HCl and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with water. The organic layer was dried, filtered and evaporated. The residue was taken up in toluene (2 L) and heated to reflux (Dean–Stark) for 20 min. After cooling, the procedure above was repeated. The reaction was left at room temperature for 10 days and then concentrated to yield 51 g of crude (+)-**33** as a colorless foam. This was dissolved in the minimum amount of chloroform and chromatographed on silica gel (1:1 v/v ethyl acetate–heptane) to yield 23 g of impure (+)-**33**. Further chromatography on silica gel (98.5:1.5 v/v chloroform–propanol) yielded 13.2 g of (+)-**33** as a crude solid.

Recrystallization from ethyl acetate–hexane produced 8.2 g of crystals shown to be a mixture of isomers by HPLC. Concentration of the mother liquors yielded 4.6 g of an oil which was shown to be 100% of pure (+)-**33** by HPLC. Chromatography (silica gel, 98:2 v/v chloroform–2-propanol) afforded 4.18 g of (+)-**33** as colorless foam, $[\alpha]^{23}_D$ = +24.53° (0.53% in $CHCl_3$).

α-Methylbenzeneacetamides. A solution of **3i** (30 g, 55.5 mmoL) in (*R*)-(+)-α-methylbenzylamine (575 mL, 4.45 mol, 98% Aldrich) was stirred overnight at room temperature. The resulting solution was diluted with ether (2 L) and washed exhaustively with 2 M HCl (4 × 500 mL), water (2 × 500 mL), and brine (2 × 500 mL). The organic extract was dried, filtered, and concentrated in vacuo to yield 28.2 g of the diastereomeric α-methylbenzylamides as a white solid, mp 174–7 °C. The α-methylbenzylamides were separated by dissolving 1.5 g of the mixture in 1.5 mL of 98:1.9:0.1 chloroform–methanol–NH_4OH and injecting onto a preparative HPLC column (silica gel, 300 mm × 41.4 mm i.d.) by a gas-tight syringe and eluting with the above solvent mixture. Diastereomer 1 eluted at 41 min. Diastereomer 2 eluted at 49 min. Center cut fractions were collected. This procedure was repeated 3 times and the like fractions combined and concentrated. Examination of each by analytical HPLC indicated that diastereomer 1 was 99.84% pure and diastereomer 2 was 96.53% pure. Each isomer was taken on separately.

(+)-(4*R*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((+)-33). To an ethanolic solution (50 mL) of diastereomer 1, [3*R*-[3*R**,5*R**]]-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrol-1-yl]-3,5-dihydroxy-*N*-[(*R*)-1-phenylethyl]-1-heptanamide, (1 g, 1.5 mmol) was added 1 N NaOH (3.0 mL, 3 mmol). The resulting solution was heated to reflux for 48 h.

The solution was cooled to room temperature and concentrated in vacuo. The residue was resuspended in water and carefully acidified with 6 N HCl. The resulting acidic solution was extracted with ethyl acetate. The organic extract was washed with water and brine, dried, filtered, and concentrated in vacuo. This residue was redissolved in toluene (100 mL) and heated to reflux with azeotropic removal of water for 3 h. This was cooled to room temperature and concentrated in vacuo to yield 1.2 g of a yellow semisolid. Flash chromatography on silica gel (2:3 v/v ethyl acetate–hexane) afforded 0.42 g of a white solid which still contained some impurities. This was rechromatographed (same system) to produce 0.1 g of essentially pure (+)-**33**, as a white foam. HPLC showed this material to be 94.6% chemically pure ($[\alpha]^{23}_D$ = +25.5° (0.51% in $CHCl_3$). The peak with a retention time of 53.46 min was tentatively assigned to an unknown diastereomer resulting from the 2% (*S*)-(−)-α-methylbenzylamine present in the Aldrich α-methylbenzylamine.

Preparation of (−)-(4*S*)-*trans*-2-(4-Fluorophenyl)-5-(1-methylethyl)-*N*,3-diphenyl-1-[(tetrahydro-4-hydroxy-2-oxo-2*H*-pyran-6-yl)ethyl]-1*H*-pyrrole-4-carboxamide ((−)-33). Carrying out the procedure described above on diastereomer 2 afforded 0.6 g of a foamy solid which was flash chromatographed on silica gel (1:1 v/v ethyl acetate–hexane) to afford 0.46 g of essentially pure (−)-**33**, as a white foam. HPLC showed this material to be 97.83% chemically pure, $[\alpha]^{23}_D$ = −24.8% (0.51% in $CHCl_3$).

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