4-Hydroxy-5,6-dihydropyrones as Inhibitors of HIV Protease: The Effect of Heterocyclic Substituents at C-6 on Antiviral Potency and Pharmacokinetic Parameters

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Due largely to the emergence of multi-drug-resistant HIV strains, the development of new HIV protease inhibitors remains a high priority for the pharmaceutical industry. Toward this end, we previously identified a 4-hydroxy-5,6-dihydropyrone lead compound (CI-1029, **1**) which possesses excellent activity against the protease enzyme, good antiviral efficacy in cellular assays, and promising bioavailability in several animal species. The search for a suitable back-up candidate centered on the replacement of the aniline moiety at C-6 with an appropriately substituted heterocyle. In general, this series of heterocyclic inhibitors displayed good activity (in both enzymatic and cellular tests) and low cellular toxicity; furthermore, several analogues exhibited improved pharmacokinetic parameters in animal models. The compound with the best combination of high potency, low toxicity, and favorable bioavailabilty was (*S*)-3-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-(2-thiophen-3-yl-ethyl)-5,6-dihydro-pyran-2-one (**13-(*S*)**). This thiophene derivative also exhibited excellent antiviral efficacy against mutant HIV protease and resistant HIV strains. For these reasons, compound **13-(*S*)** was chosen for further preclinical evaluation.

It has become fashionable to think of HIV infection as a chronic condition, much like diabetes, rather than the inevitably fatal scourge depicted in the lay press only five years ago. The introduction of potent antiretroviral chemotherapies has revolutionized HIV/AIDS care and dramatically impacted the life span and lifestyle of the HIV patient. In particular, the combination of protease inhibitors with reverse transcriptase inhibitors has become a standard of front-line therapy in the developed world.[1] Despite the hope and promise these agents have engendered, very real problems exist with the current antiviral armamentarium, especially with the protease inhibitors: low bioavailability,[2] side effects such as lipodystrophy[3] and toxicity,[4] and drug interactions.[5] More significantly, the serious threat posed by resistant strains of HIV[6] necessitates continued research for novel inhibitors of viral replication. Indeed, it has been estimated that only half of those patients starting a regimen containing protease inhibitors actually achieve a sustained suppression of the virus;[7] the outlook is particularly grim for treatment-experienced patients considering salvage therapy.[8,9] In addition, the high cost of drug has made these regimens prohibitively expensive for the vast majority of AIDS sufferers worldwide.

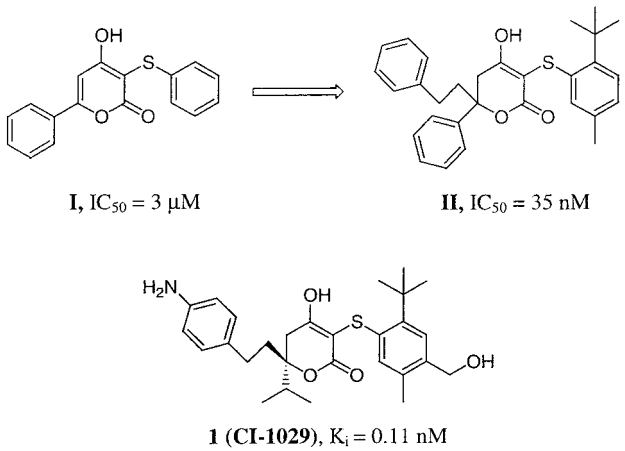

Figure 1.

Previous reports from our laboratory[10] and others[11] have identified the 4-hydroxy-5,6-dihydropyrones as a novel class of non-peptidic protease inhibitors. Optimization of the enzymatic potency of pyrone **I** (Figure 1), identified from a mass screen, was achieved via extensive synthetic modification and concomitant X-ray crystallographic studies. X-ray crystal structures of the resulting dihydropyrones **II** bound to the protein (Figure 2) revealed that the enolic hydroxyl group of the dihydropyrone core forms hydrogen bond(s) with the aspartate residues at the cleavage site while the lactone moiety interacts with the Ile residues in the flap region. Moreover, the groups appended to the 6-position occupy the S_1 and S_2 pockets while the phenyl substituents on

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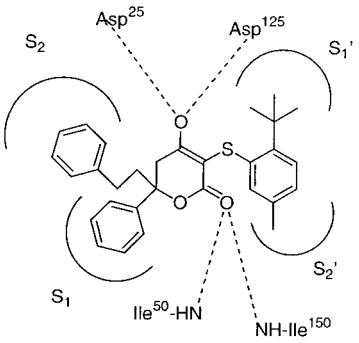


Figure 2. X-ray crystal structure of prototypical dihydropyrone.

the *S*-phenyl moiety at C-3 filled the S_1' and S_2' pockets. Although the prototypic dihydropyrone **II** displayed excellent efficacy in enzyme assays, no significant antiviral activity was observed in cell culture. Attempts to enhance the antiviral potency by manipulating the lipophilicity and polarity of the target compounds resulted in the discovery of dihydropyrone **1** (Figure 1) This agent, CI-1029, demonstrated excellent enzyme activity against the HIV protease, but more importantly displayed an EC_{50} of 200 nM with a therapeutic index of >1000. In addition, CI-1029 also exhibited good pharmacokinetic parameters, favorable activity against mutant HIV PR and against resistant HIV strains, and little interaction with cytochrome P-450 (30% inhibition at 100 μM for 3A4)—all characteristics of a promising preclinical candidate.

With one development candidate in hand, efforts were concentrated on the discovery of an appropriate second-generation agent. Ideally, this back-up candidate would display enhanced cellular potency and improved pharmacokinetic parameters when compared to CI-1029, while retaining a favorable side effect profile. Of particular importance was the identification of a new agent without the aniline moiety at C-6, since N-acetylation of the aniline group presents a likely avenue for metabolic instability. Toward this end, a series of dihydropyrones was synthesized in which a heterocyclic group was introduced into the S_2 pocket via appropriate substitution at the C-6 position. In this paper we will discuss the synthesis, antiviral activity, and preliminary pharmacokinetics for this series and the discovery of another preclinical candidate, derivative **13-(*S*)**.

Chemistry

The synthesis of the target compounds requires the preparation of the thiotosylate side chain[12] and the dihydropyrone nucleus,[10] both of which have been reported previously. In general, the dihydropyrone core was prepared from the requisite ketone and the dianion of methyl acetoacetate. These heterocyclic ketones **B** (listed in Table 1) were synthesized via two complementary routes as summarized in Scheme 1. In the first approach, the starting aldehyde was condensed with a triphenyl arsenate salt, prepared from the reaction of 1-chloro-3-methyl-2-butanone and triphenyl arsine,[13] to give the enone **A**; alternatively, the aldehyde could be reacted with 3-methyl-2-butanone and barium hydroxide under standard Claisen-Schmidt conditions. In either case, the resulting enones **A** were then reduced catalytically to give the target ketones **B**. In a complementary approach (also Scheme 1), the halogenated heterocycle **C** was reacted with the allylic alcohol in the presence of palladium acetate and various cofactors. This particular strategy obviates the need for a reduction step in that the desired ketone is produced in moderate to good yield in one step.[14] Conversion of these heterocyclic ketones to the penultimate dihydropyrones **D** was accomplished smoothly with little deviation from the previously reported methods[15] and is summarized in Table 2.

Several analogues containing a methylene alcohol (CH_2OH) in the heterocyclic ring were also prepared. In general, the alcohol moiety was protected as a *tert*-butyl-dimethylsilyl ether during the early steps of the synthesis and then removed just prior to the ring closure to dihydropyrone **D**. Deprotection was easily effected via treatment with fluoride ion, and subsequent purification was not necessary.

The majority of the 4-hydroxy-5,6-dihydropyrones synthesized for this study were racemic mixtures at the C-6 position. For those compounds of particular interest, the enantiomerically pure isomers were prepared as shown in Scheme 2. In this route, the intermediate ketone **B** is reacted with the anion of *tert*-butyl acetate to give intermediate ester **E**. Resolution of the mixture of stereoisomers was accomplished via chromatographic separation on a Chiralpak column to give esters **E-(*S*)** and **E-(*R*)**. These esters were hydrolyzed to the requisite acids (**F-(*S*)** and **F-(*R*)**) which were then elaborated to the β-ketoesters. Treatment of β-ketoesters **G-(*S*)** and **G-(*R*)** with dilute base gave the desired 4-hydroxy-5,6-dihydropyrones (**D**) as before.

The requisite thiotosylate contains the benzyl alcohol moiety in the phenyl ring at C-3. Its preparation from the phenol has been described in our earlier reports.[12,15] Reaction of the dihydropyrone nucleus with excess thiotosylate and several equivalents of potassium carbonate in DMF gave, after purification, target compounds **2**−**35** (Table 3.)

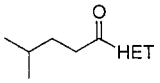
Biological Methods

The compounds in this study were tested for their inhibition of HIV protease using an HPLC assay at pH 6.2 as reported previously[16] and as outlined in the Experimental Section. Cellular anti-HIV activity was measured at Southern Research Institute in an assay using HIV-IIIB-infected human lymphocyte-derived CEM cells.[17] EC_{50} refers to the concentration of drug at which 50% of the cells are protected against the cytopathic effects of HIV; TC_{50} refers to the concentration of drug which elicits cytotoxicity in 50% of CEM cells uninfected with HIV. Enzymatic K_i's and cellular EC_{50}'s and TC_{50}'s are reported in Table 3.

Results and Discussion

CI-1029 (compound **1** in Table 3) possessed all the desirable attributes of a promising preclinical candidate but also a potentially serious liability. The amino group in the phenethyl chain at C-6 presents a likely site for metabolism and unwanted derivatization. Indeed, metabolic profiling of this compound in several species revealed that 20−40% of the compound was acylated (unpublished results.) Therefore, one of the primary goals in the search for a second-generation agent was

Table 1. Analytical Data for Intermediate Ketones B



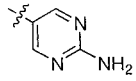
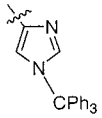
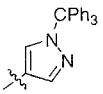
cmpd	HET	Source of St. Mat.[a]	Method of Prep.[b]	Purification	Yield (%)
B-1		Comm.	A	chrom. 2:1:1 EtOAc: CH_2Cl_2:hex	76
B-2		Comm.	C	chrom. 98:2 CH_2Cl_2:MeOH	79
B-3		Comm.	A	chrom. 98:2 CH_2Cl_2:MeOH	87
B-4		Comm.	C	chrom. 98:2 CH_2Cl_2:MeOH	60
B-5		Comm.	C	chrom. 98:2 CH_2Cl_2:MeOH	50
B-6		Comm.	A	chrom. 98:2 CH_2Cl_2:MeOH	86
B-7		from B-6	Expt.	chrom. 9:1 hex: EtOAc	99
B-8		Comm.	C	chrom. 9:1 hex: EtOAc	42
B-9		Comm.	C	chrom. 95:5 hexane:EtOAc	17
B-10		Comm.	B	chrom. 50:50 CH_2Cl_2:hexane	26
B-11		from B-10	Expt	chrom. 99:1 CH_2Cl_2:MeOH	74
B-12		Comm.	D	chrom. 95:5 hexane:EtOAc	24
B-13		Comm.	D	chrom. 95:5 hexane:EtOAc	38
B-14		Comm.	A	chrom. 1:1 hexane:EtOAc	34
B-15		Ref. 21	A	chrom. 3:1 hexane:EtOAc	55
B-16		Ref. 21	A	chrom. 2:1 hexane:EtOAc	35
B-17		Ref. 22.	D	chrom. 9:1 hexane:EtOAc	39
B-18		Comm.	D	chrom. 9:1 hexane:EtOAc	14

Table 1 (Continued)

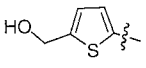
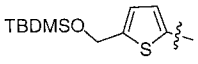
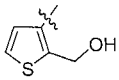
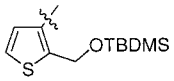
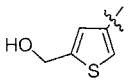
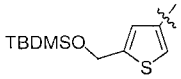
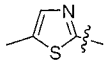
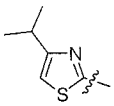
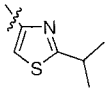
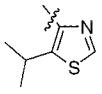
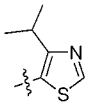
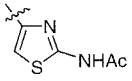
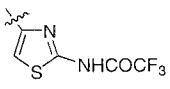
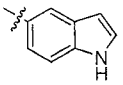
cmpd	HET	Source of St. Mat.[a]	Method of Prep.[b]	Purification	Yield (%)
B-19		Expt.	D	chrom. 99.5:0.5 CH_2Cl_2:MeOH	60
B-20		from B-19	E	chrom 95:5 hex:EtOAc	68
B-21		Expt.	D	chrom. 99.5:0.5 CH_2Cl_2:MeOH	37
B-22		from B-21	E	none	
B-23		Ref. 23	D	chrom 99:1 CH_2Cl_2:MeOH	21
B-24		from B-24	E	chrom. 95:5 hex:EtOAc	84
B-25		Ref. 24	A	chrom. 2:1 hexane:EtOAc	44
B-26		Ref. 24	A	chrom. 2:1 hexane:EtOAc	40
B-27		Expt.	A	chrom. 2:1 hexane:EtOAc	46
B-28		Expt.	A	chrom. 3:1 hexane:EtOAc	59
B-29		Ref. 25	A	chrom. 2:1 hexane:EtOAc	76
B-30		Expt.	A	chrom. 3:1 hexane:EtOAc	59
B-31		Expt.	A	no purification necessary	74
B-32		Expt.	A	chrom. 3:1 hexane:EtOAc	54
B-33		Expt.	A	chrom. 2:1 hexane:EtOAc	71
B-34		Ref. 26	A	chrom. EtOAc	17
B-35		from B-34	Expt.	chrom. EtOAc	
B-36		Ref. 27	A	chrom. EtOAc	75

Table 1 (Continued)

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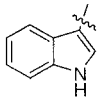
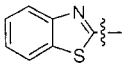
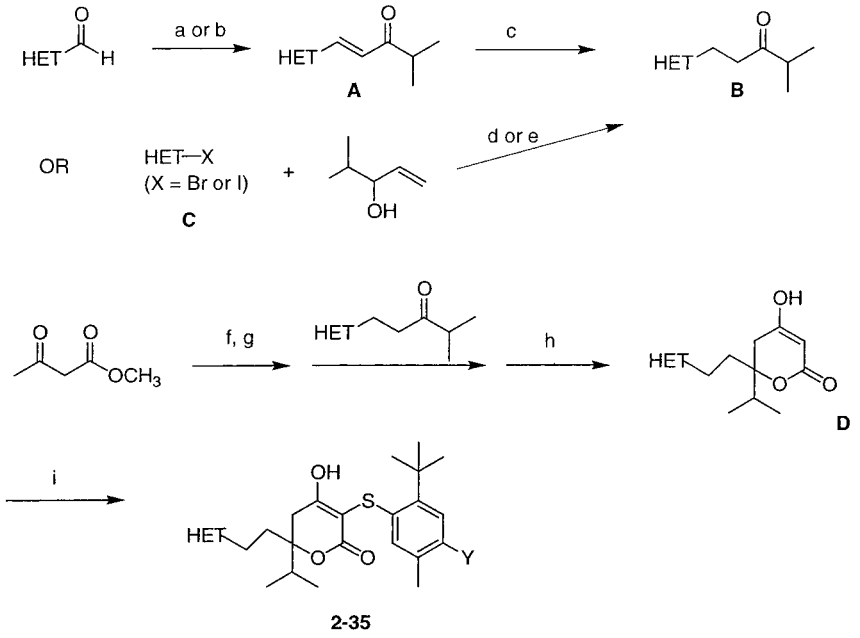
B-37		Comm.	A	chrom. 2:1 hexane:EtOAc	45
B-38		Ref. 28	A	chrom. 2:1 hexane:EtOAC	43

[a] Comm. refers to commercially available material; Expt. denotes that the preparation of the starting material can be found in the Experimental Section. [b] Letter refers to the general method found in the Experimental Section, Figure 1.

Scheme 1. Preparation of Racemic Dihydropyrones[a]



[a] (a) $AsPh_3CH_2COCH(Me)_2$, K_2CO_3, aq CH_3CN; (b) $CH_3COCH(Me)_2$, $Ba(OH)_2$; (c) H_2, $Pd/BaSO_4$; (d) NaI, $NaHCO_3$, PPh_3, $Pd(OAc)_2$, DMF; (e) $(n\text{Bu})_4NCl$, $NaHCO_3$, pyrrolidine, DMF, $Pd(OAc)_2$; (f) NaH; (g) *n*BuLi; (h) OH^-, then H^+; (i) thiotosylate, K_2CO_3, DMF.

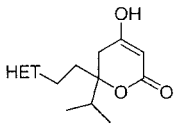
the replacement of the aniline moiety with a more metabolically stable functionality.

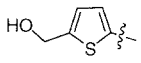
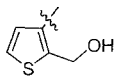
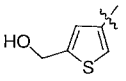
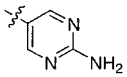
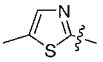
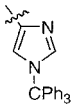
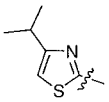
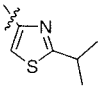
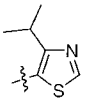
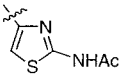
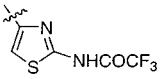
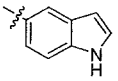
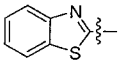
Previous SAR studies and X-ray analyses indicated that the S_2 pocket of the protease enzyme could tolerate a wide variety of substituents without subsequent loss of enzyme potency. Indeed, past increases in enzyme potency did not necessarily correlate with increased antiviral potency until substantial changes in polarity and lipophilicity were introduced.[15,18] For this reason, we theorized that an appropriate heterocyclic replacement of the 4-aminophenyl group at S_2 could effect the same change of polarity and/or lipophilicity without the use of an aniline. In other words, we hoped to modulate the physical properties of these analogues without affecting the enzyme potency or the antiviral efficacy already achieved by CI-1029.

Therefore, a series of dihydropyrones containing a heterocycle in the S_2 pocket was synthesized and is summarized in Table 3. For these analogues, the substitution at C-3 was restricted to the 2′-*tert*-butyl-4′-(hydroxymethyl)-5′-methylphenyl moiety previously used for lead compound CI-1029. Prior work in our laboratory had established the superiority of this particular group at C-3, although an amino group at the 4′ position has also been shown to confer good activity. However, since our intent was to remove any potential metabolic liability associated with an aniline group, introduction of yet another aniline into the 3-position would be undesirable. The current lead compound, compound **1** (CI-1029), was used as a benchmark for all potential back-up candidates. Of note is the chirality issue: **1** exists as a single enantiomer whereas all of the newly synthesized comparitors were tested as racemic mixtures. For the sake of comparison, data for racemic **1** (designated as **1-(±)**) are also included in Table 3.

Compounds **2** through **8** contain a nitrogen heterocycle (pyridine, pyrimidine, imidazole, and pyrazole) in the region previously occupied by the aminophenyl group. In the case of pyrazole **7**, the enzyme activity remained essentially equipotent with that of racemic **1-(±)**; in all other cases, the potency of the nitrogen analogues decreased by a least 2-fold (and by as much as 700-fold in the case of **8**). More important was the significant loss in antiviral potency: although pyridine analogues **2** ($EC_{50} = 1.5\ \mu M$), **3** ($EC_{50} = 0.9\ \mu M$), and **4** ($EC_{50} = 1.5\ \mu M$) and pyrimidine **5** ($EC_{50} = 1.2\ \mu M$) were modestly active, several derivatives showed more dra-

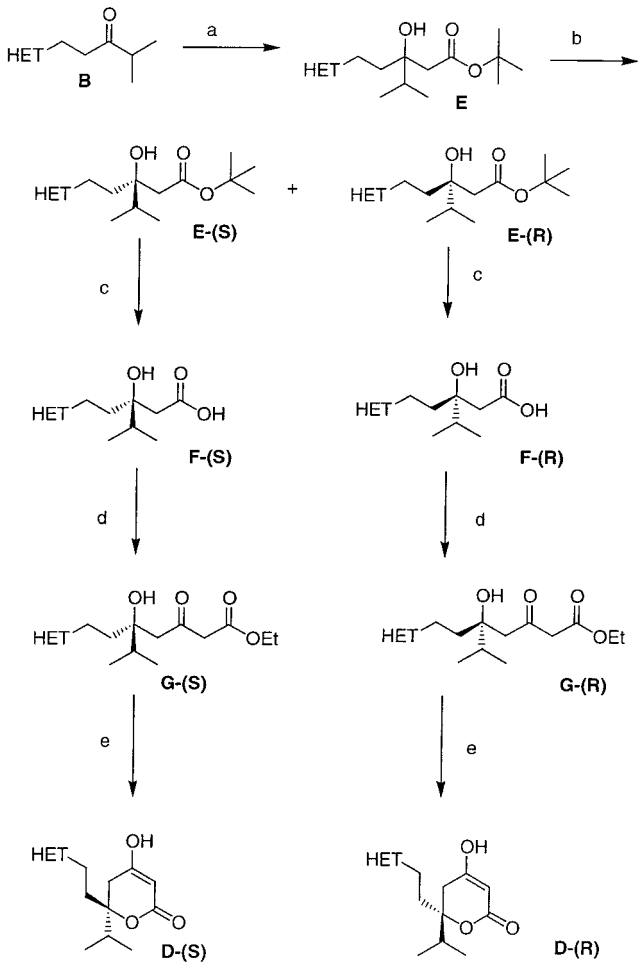
Table 2. Analytical Data for Intermediate Dihydropyrones D



cmpd	HET	Yield[a]	Purification[b]	cmpd	HET	Yield[a]	Purification[b]
D-1		70	trit. Et_2O:EtOAc	**D-18**		43 (3 steps)	none
D-2		44	chrom. 99:1 CH_2Cl_2:MeOH	**D-19**		54 (3 steps)	recryst. from EtOAc
D-3		69	trit. Et_2O:EtOAc	**D-20**		52 (3 steps)	recryst. from CH_2Cl_2:Et_2
D-4		25	chrom. 95:5 CH_2Cl_2:MeOH	**D-21**		47	chrom. 95:5 CH_2Cl_2:MeOH
D-5		19	trit. EtOH	**D-22**		72	chrom. 95:5 CH_2Cl_2:MeOH
D-6		73	none	**D-23**		68	chrom. 95:5 CH_2Cl_2:MeOH
D-7		50[c]	chrom. 95:5 CH_2Cl_2:MeOH	**D-24**		48	chrom. 95:5 CH_2Cl_2:MeOH
D-8		61	chrom. 99:1 CH_2Cl_2:MeOH	**D-25**		72	chrom. 95:5 CH_2Cl_2:MeOH
D-9		87	trit. Et_2O:EtOAc	**D-26**		45	chrom. 95:5 CH_2Cl_2:MeOH
D-10		94	none	**D-27**		72	chrom. 95:5 CH_2Cl_2:MeOH
D-11		87	none	**D-28**		56	chrom. 95:5 CH_2Cl_2:MeOH
D-12		92	trit. with ether	**D-29**		63	chrom. 95:5 CH_2Cl_2:MeOH
D-13		56	chrom. 95:5 CH_2Cl_2:MeOH	**D-30**		72	trit. hexane
D-14		50	chrom. 95:5 CH_2Cl_2:MeOH	**D-31**		62	chrom. 95:5 CH_2Cl_2:MeOH
D-15		57	chrom. 95:5 CH_2Cl_2:MeOH	**D-32**		59	none
D-16		85	recryst. from Et_2O:hex	**D-33**		72	chrom. EtOAc
D-17		66	trit. with ether	**D-34**		56	chrom. 95:5 CH_2Cl_2:MeOH

[a] Yield calculated from the appropriate ketone precursor in Table 1; includes protection/deprotection steps where necessary. [b] Trituration (trit) refers to grinding of the solids under solvent to produce a fine powder. [c] Another 25% of the *N*-trityl product (mp 66−70 °C) was also obtained.

Scheme 2. Preparation of Chiral Dihydropyrones[a]



[a] (a) LDA, *tert*-butyl acetate; (b) separation via Chiralpak AD; (c) NaOH; (d) CDI, then $Mg(O_2CCH_2CO_2Et)_2$; (e) OH^-, then H^+.

matic 100-fold losses in activity (for example, imidazole **8**, EC_{50} = 89 μM). Overall, none of these nitrogen heterocycles were equipotent with parent compound **1** although all derivatives displayed low toxicity.

Simple heterocycles—such as furan **(9**−**10**), tetrahydrofuran (**11**), thiophene (**12**−**13),** and thiazole **(14**−**16)**—were also prepared, with more encouraging results. With one exception (compound **11**), these analogues displayed excellent activity against the HIV-1 protease enzyme, with a K_i of 1 nM or lower. Several compounds also showed encouraging antiviral activity: thiophene **12** (EC_{50} = 0.50 μM) and its regioisomer **13** (EC_{50} = 0.30 μM) were of particular promise. Both derivatives displayed good antiviral activity albeit with a slight increase in toxicity (TC_{50} = 81 μM and 110 μM, respectively) when compared to CI-1029 and its racemic parent. It is interesting to note that regiochemistry exerted little influence over the antiviral activity in both the furan and the thiophene series, in that the activity of the 2-furan **9** (EC_{50} = 0.75 μM) did not vary significantly from the 3-furan **10** (EC_{50} = 1.0 μM). However, greater variation in activity was observed for the thiazole regioisomers in which the 2-isomer **14** (EC_{50} = 0.7 μM) was two times more active than the 5-isomer **16** (EC_{50} = 1.9 μM) in the cellular assay and 4 times more active than the 4-isomer **15** (EC_{50} = 2.8 μM). In general, these thiazoles were less toxic (TC_{50} > 200 μM) than the thiophene analogues and similar to the original lead.

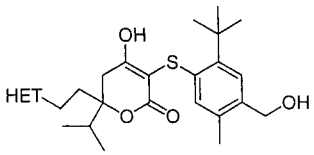
Prior experience in the SAR of the 6-position suggested that further elaboration of the heterocycle ring might prove advantageous in fully occupying the S_2 pocket (results not shown.) For this reason, a number of thiophene and thiazole derivatives were made in which alkyl groups were appended to various positions of the heterocycle. In the case of the thiophene, these new methylated derivatives (**17** and **18)** were essentially equipotent to the parent unmethylated compounds; however, in both cases the TC_{50} dropped significantly. Again, the presence of a single methyl group in the thiazole series engendered a more dramatic effect on the antiviral potency than it did in the thiophene series. The EC_{50}'s of the five various methylthiazole isomers varied from 0.37 to 4.5 with a similar range of enzymatic K_i's, all dependent on the positions of the ethylene linker and the methyl group. The most potent of these thiazole derivatives, the 4-methyl compound **26**, possessed an EC_{50} of 0.37 μM and an excellent TC_{50} of 164 μM. For this reason, the 4-methyl-5-thiazole derivative emerged as a potential back-up to CI-1029 along with the simple thiophene analogues mentioned earlier.

Several additional substituted thiazole derivatives were also synthesized. Enlarging the alkyl group found in the methylthiazole series to an isopropyl moiety resulted in compounds **27**−**30**. Unfortunately the larger group proved deleterious to cellular activity, since the isopropyl analogues were much less active and more toxic than the methyl comparitors; apparently, the steric requirements of the S_2 pocket do not allow for such a large hydrophilic group. Also of note was the influence of a 2-amino group on the activity of the thiazole analogue. While the 2-acetylamino analogue **31** (EC_{50} = 23 μM) displayed a 10-fold decrease in antiviral potency when compared to the 2-hydrogen parent **15** (EC_{50} = 2.8 μM), the 2-amino derivative **32** (EC_{50} = 3.5 μM) was essentially equipotent with the unsubstituted parent. More importantly, the presence of the amino group did not engender any appreciable improvement in pharmacokinetic parameters (results not shown.)

Earlier work in our laboratories identified the benzyl alcohol moiety as a group that imparted good activity when placed on the phenyl group at C-3. When this same benzyl alcohol group was affixed to a phenyl ring at C-6—usually ortho to the ethylene linker—a boost in activity was also seen, although not of the magnitude observed for the 3-position isomer (data not shown). For this reason, a series of thiophene analogues (compounds **19**−**21**, Table 3) was prepared in which a hydroxymethyl substituent was appended to various positions of the thiophene ring. The most potent of these hydroxymethyl thiophenes was compound **20**, with an EC_{50} of 0.92 μM and a TC_{50} of 200 μM, but in general these analogues showed no advantages over the unsubstituted thophenes. It is interesting to note that the analogue with the best potency (compound **20**) contains the hydroxymethyl adjacent to the ethylene spacer − the same orientation seen in the series containing a phenethyl group at C-6.

A limited number of fused heterocyclic analogues—namely indoles and benzthiazoles—were also prepared.

Table 3. Chemical and Biological Data for 4-Hydroxy-1,4-dihydropyrones



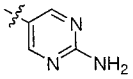
cmpd	HET	m.p., °C	Analysis[a]	IC_{50} (nM)[b]	EC_{50} (μM)[c]	TC_{50}(μM)[d]
1-(S) (CI-1029)	Ph-NH_2	Ref. 18		0.11	0.20	210
1-(±)	Ph-NH_2	Ref. 15		0.43	0.50	>100
2		146-155	$C_{27}H_{35}NO_4S \cdot 1.24\ H_2O$	1.2	1.5	249
3		122-125	$C_{27}H_{35}NO_4S \cdot 0.47\ H_2O$	0.94	0.9	216
4		140-155	$C_{27}H_{35}NO_4S \cdot 1.02\ H_2O$	1.5	1.5	296
5		221-223	$C_{26}H_{34}N_2O_4S \cdot 0.4\ H_2O$	17	1.2	>200
6		145-148	$C_{26}H_{35}N_3O_4S$		5.7	>200
7		136-138	$C_{25}H_{34}N_2O_4S$	0.28	5.6	320
8		205	$C_{25}H_{34}N_2O_4S \cdot 1.6\ H_2O$	70	89	200
9		64-110	$C_{26}H_{34}O_5S$	0.78	0.75	190
10		62-70	$C_{26}H_{34}O_5S \cdot 0.37\ H_2O$	0.34	1.0	199
11		57-59	$C_{26}H_{38}O_5S$	5.0		
12		73-77	$C_{26}H_{34}O_4S$	0.35	0.5	81
13		63-70	$C_{26}H_{34}O_4S_2 \cdot 0.39\ H_2O$	0.17	0.30	110
13-(S)		73-82	$C_{26}H_{34}O_4S_2 \cdot 0.40\ H_2O$	0.13	0.12	91
13-(R)		65-73	$C_{26}H_{34}O_4S_2$	11.5	14	95
14		108-110	$C_{25}H_{33}NO_4S_2 \cdot 0.2H_2O$	0.57	0.7	216
15		115-118	$C_{25}H_{33}NO_4S_2 \cdot 1.2H_2O$	1.3	2.8	141

Table 3 (Continued)

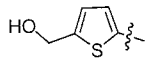
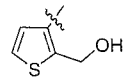
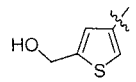
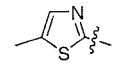
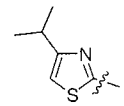
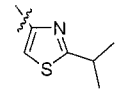
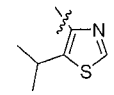
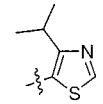
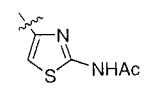
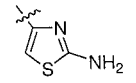
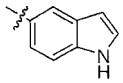
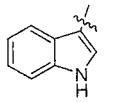
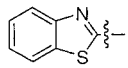
cmpd	HET	m.p., °C	Analysis[a]	IC_{50} (nM)[b]	EC_{50} (μM)[c]	TC_{50}(μM)[d]
16		120-124	$C_{25}H_{33}NO_4S_2 \cdot 0.2H_2O$	0.24	1.9	229
17		86-90	$C_{27}H_{36}O_4S_2$		0.28	80
18		115	$C_{27}H_{36}O_4S_2$	0.41	0.26	51
19		110-117	$C_{27}H_{36}O_5S_2$	0.58	2.5	182
20		87-90	$C_{27}H_{36}O_5S_2 \cdot 0.52\ H_2O$	14	0.92	200
21		76-80	$C_{27}H_{36}O_5S_2 \cdot 0.88\ H_2O$	0.19	18	210
22		98-100	$C_{26}H_{35}NO_4S_2 \cdot 0.2H_2O$	0.45	0.8	171
23		103-105	$C_{26}H_{35}NO_4S_2$	1.9	1.9	210
24		118-121	$C_{26}H_{35}NO_4S_2 \cdot 0.5H_2O$	13	4.5	210
25		105-108	$C_{26}H_{35}NO_4S_2$	1.3	1.8	208
26		138-141	$C_{26}H_{35}NO_4S_2 \cdot 0.5H_2O$		0.37	164
27		95-97	$C_{28}H_{39}NO_4S_2 \cdot 0.3H_2O$	14	33	84
28		97-100	$C_{28}H_{39}NO_4S_2 \cdot 0.3H_2O$	1.6	23	91
29		108-112	$C_{28}H_{39}NO_4S_2 \cdot 0.6H_2O$	5.8	10	52
30		109-112	$C_{28}H_{39}NO_4S_2 \cdot 0.25H_2O$	0.8	1.2	102
31		128-130	$C_{27}H_{36}N_2O_5S_2 \cdot 0.5\ H_2O$	18	23	210
32		208-210	$C_{25}H_{34}N_2O_4S_2$	0.95	3.5	>200

Table 3 (Continued)

cmpd	HET	m.p., °C	Analysis[a]	IC_{50} (nM)[b]	EC_{50} (μM)[c]	TC_{50}(μM)[d]
33		94-96	$C_{30}H_{37}NO_4S \cdot 0.6H_2O$	0.98	0.68	46
34		114-117	$C_{30}H_{37}NO_4S \cdot 0.3H_2O$	0.72	0.37	46
35		105-107	$C_{29}H_{35}NO_4S_2 \cdot 0.2H_2O$	1.4	1.5	62

[a] All compounds were analyzed for C, H, and N and had results +0.4% of theoretical values. [b] Enzyme inhibition was determined as described in the Experimental Section. [c] Antiviral activity in HIV infected CEM cells. EC_{50} refers to the effective concentration at which 50% of the cells are protected from cytopathic effects. [d] Toxicity measured in CEM cells in the absence of virus.

Table 4. Pharmacokinetic Data for Heterocyclic Dihydropyrones in Mice[a]

cmpd	C_{max} (μM)	T_{max} (h)	$T_{1/2}$ (h)	AUC (μM h/mL)
1-(*S*)	26.5	0.5	2.2	82
1(±)	23	0.5	2.2	42
3	45.8	0.5	7.3	143
10	54.4	0.5	5.6	241
13	39.6	0.5	3.5	221
14	33	0.5	3.3	132

[a] All compounds were dosed at 25 mg/kg in a vehicle consisting of 20% 0.1 N NaOH/80% 0.5% methylcellulose. Values are from a pool of five mice.

Table 5. Pharmacokinetic Parameters for Heterocyclic Dihydropyrones in Rats[a]

cmpd	C_{max} (μM/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (μg h/mL)
1-(*S*)	7.2	0.5	3.7	11.4
13	11.2	0.5	9.4	21
13-(*S*)	14.7	0.5	11.5	22.5
14	2.7	0.25	12.2	10
26	0.77	0.25	ND	ND

[a] All compounds were dosed at 10 mg/kg using a capsule or a solution buffered to pH 7.4. Values are an average of two animals.

While all these derivatives possessed moderate to good activity (for example, indole **34** with an EC_{50} of 0.37 μM), they also displayed increased toxicities of 40−60 μM.

The racemic analogue of our lead compound, CI-1029, exhibited excellent cellular potency (EC_{50} = 0.5 μM) and low toxicity in cell culture (TC_{50} > 100 μM.)[17] Using these numbers as a benchmark, several derivatives containing a heterocycle at C-6 also displayed excellent enzyme activities, good antiviral efficacy, and low toxicity. These analogues—both racemic—included the 3-thiophene **13** (EC_{50} = 0.3 μM, TC_{50} = 110 μM) and the 4-methyl-5-thiazole **26** (EC_{50} = 0.37 μM, TC_{50} =164 μM). Although other analogues also possessed excellent antiviral activity (for example, thiophene **17** and indole **34**), these compounds also exhibited unacceptable toxicity (TC_{50} = 80 μM and 46 μM, respectively.) Therefore, further assessment of analogues **13** and **26** was warranted.

Pharmacokinetic parameters for a variety of heterocyclic derivatives (including thiophene **13** and thiazole **26**) were measured in mice and rats and were compared to the racemic and chiral lead CI-1029, where possible. Mice were dosed po at 25 mg/kg using a vehicle of 20% 0.1 N NaOH in 0.5% methylcellulose, and plasma levels were measured via an HPLC assay. Similarly, rats were dosed po at 10 mg/kg using a capsule or solution buffered to pH 7.4. The results are summarized in Tables 4 (mice) and 5 (rats).When assayed in mice, the heterocyclic derivatives all displayed improvements in C_{max} and a concomitant improvement in AUC. Although pyridine **3** and furan **10** showed promising improvements in half-life, most of the new analogues were essentially equivalent in the mouse model.

In the rat, however, the thiophene compound **13** appears substantially better than the other comparitors, with an especially dramatic improvement in C_{max} (0.77 μM for thiazole **26** versus 11.2 μM for thiophene **13**.) Interesting to note is the effect of a single methyl group on the activity of thiazole derivatives: 2-thiazole derivative **14** has a C_{max} that is 3.5 times higher than that of the 4-methyl-5-thiazole **26.** Thiophene **13** also exhibits a significant improvement in pharmacokinetics when compared to CI-1029 (compound **1**). Most notable were the changes in $T_{1/2}$ (9.4 for **13** vs 3.7 for **1**) and AUC. This enhancement in pharmacokinetic properties, along with its excellent antiviral efficacy and low toxicity, led us to choose thiophene **13** for further study.

The enantiomers of racemate **13** were synthesized as outlined in Scheme 2; the activities of the individual stereoisomers are listed in Table 3. As expected from analogy with previous series, the more active isomer possesses the *S* stereochemistry: compound **13-(*S*)** was 100 times more potent in both the HIV-protease assay and the cellular antiviral screen than its enantiomer **13-(*R*)**. The more active isomer was assayed for pharmacokinetic properties in the rat model and, as expected, demonstrated comparable properties to that of the racemate **13**. However, the supremacy of the chiral thiophene **13-(*S*)** over the prior lead compound can best be seen in the dog model, for which the data is summarized in Table 6. By every measure, the optically pure thiophene displayed superior pharmacokinetic properties with an increased half-life, excellent bioavailability, and an encouraging time above the EC_{90}.

Further preclinical profiling of thiophene **13-(*S*)** was undertaken by measuring cytochrome P-450 inhibition and antiviral activity in the presence of serum. Incubation of compound **1-(*S*)** with human liver microsomes and a series of major P-450 isoenzyme selective probes revealed no inhibition of CYP3A4 at 1 and 10 μM and

Table 6. Pharmacokinetic Parameters for Selected Dihydropyrones in Dogs[a]

	C_{max} (μg/mL)	$T_{1/2}$	AUC (μg h/mL)	hours above the EC_{90}	bioavailability (%)
1-(*S*)	77	1.2	113	4	33
13-(*S*)	152	5.4	592	9	88

[a] Animals were dosed at 10mg/kg, and the vehicle was the sodium salt dissolved in normal saline for **1** and free acid dissolved in 0.1 NaOH (buffered to pH 10) for **13-(*S*)**. Values are an average from two animals.

Table 7. Antiviral Activity of Selected Dihydropyrones against HIV Protease-Resistant Strains

	fold increase in EC_{50} for inhibitors			
protease amino acid substitutions	IDV[a]	RTV[b]	**1-(*S*)**	**13-(*S*)**
V31I, L10I, I15V, K20R, M36I, S37N, R41K, G48V, I54T/I, L63T, A71V, T74A, V82A/V, 193L	19	38	1	2
V3I, L10I, K20R, E35D, M36I, S37D, R41K, G48V, L63C, A71V, I72T, V82A/V, 193L	3	9	1	1
V31, L10I, L19I, S37Q, M46L, I54V, R57K, L63P, A71V, V82A, L90M	5	39	1	2
V3I, L10I, I15V, K20R, E35D, M36I, S37K, R41N, K43T/K, M46I, L63P, H69K, A71V, T74S, V82F, N88E, L89M, L90M, I93L	40	23	<1	2
V3I, L10I, 115V, K20I, L24I, M36I, S37N, I54V, R57K, L63P, A71V, V82A	17	44	<1	<1

[a] Indinavir. [b] Ritonavir.

very little inhibition (30%) at 100 μM. Results for thiophene **13-(*S*)** were strikingly similar: no inhibition at 1 and 10 μM with slight inhibition (34%) at 100 μM. This dearth of activity even at high concentrations bodes well for **13-(*S*)** in the area of cytochrome inhibition and potential drug interactions. In addition, dihydropyrones **1-(*S*)** and **13-(*S*)** were assayed for antiviral activity in the presence of 30% human serum in order to ascertain the effect of protein binding on efficacy. Both analogues did lose activity such that the two were essentially equipotent in the presence of serum (EC_{50} for **1-(*S*)** = 6.31 μM and EC_{50} for **13-(*S*)** = 10.4 μM.)

The problems stemming from drug-resistant strains of HIV have emerged as the most serious dilemma facing clinicians and patients today. To help ameliorate this problem, many pharmaceutical companies are developing structurally dissimilar protease inhibitors in the hopes of producing dissimilar resistance patterns. Toward this goal, dihydropyrones **1-(*S*)** and **13-(*S*)** were assayed against a panel of protease inhibitor-resistant HIV strains. The antiviral potency was measured in an in vitro assay in HIV-infected PBMC cells, and the results are summarized in Table 7; the data are reported as fold increases in activity. In general, both CI-1029 (**1-(*S*)**) and thiophene **13-(*S*)** displayed excellent activities against strains of virus already resistant to the clinical agents indinavir and ritonavir. In all cases the dihydropyrone derivatives show a reduction in susceptibility that is 2-fold or less.

In conclusion, a series of dihydropyrones was synthesized in which a heterocycle was substituted for the aminophenyl substituent found in lead compound CI-1029. From this series, a new preclinical candidate, compound **13**, was identified which contains a thiophene at the 6-position. The chiral form **(13-(*S*))** was then synthesized and assayed for potency against the HIV protease enzyme, antiviral activity in cell culture, and pharmacokinetic parameters in mice, rats, and dogs. In all cases, the thiophene compound proved superior to the prior lead compound, displaying excellent antiviral efficacy (EC_{50} = 0.12 μM), low toxicity (TC_{50} = 92 μM), and promising bioavailablity across all species tested. Also encouraging was the activity against protease-resistant strains of HIV. The ease of synthesis, low molecular weight, and presence of a single chiral center of this agent also bode well for future success. For these reasons, compound **13-(*S*)** was chosen for further preclinical studies.

Experimental Section

Enzyme Inhibition Assay. For determination of IC_{50} values, affinity-purified HIV-1 protease (Bachem Bioscience; 1.1 nM) was added to a solution of the following: the inhibitor, 40 μM peptide substrate (His-Lys-Ala-Arg-Val-Leu-(p-NO_2-Phe)-Glu-Ala-Nle-Ser-NH_2; Bachem Bioscience), and 1.0% DMSO in assay buffer (1.0 mM dithiothreitol, 80 mM MES, 160 mM NaCl, 1.0 mM EDTA, 0. 1% poly(ethylene glycol) (MW 8000), pH 6.2 at 25 °C). The final volume was 100 μL; final concentration of HIV protease was 1.5 nM. The solution was mixed, incubated for 60 min at 37 °C, and then quenched with trifluoroacetic acid (2% final). In this assay, the Leu-(p-NO_2-Phe) bond of the substrate was cleaved by the enzyme, and the substrate and cleavage products were separated by reverse-phase HPLC. Absorbance was measured at 220 nm, peak areas were determined, and percent conversion to product was used to calculate percent control (= [%conversion (+inhibitor)/%conversion (−inhibitor)] × 100).

Chemistry. Melting points (mp) were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra (^{1}H NMR) were obtained on a Varian Unity 400 MHz NMR using TMS as an internal standard. Chemical shifts are reported in ppm. Mass spectral data were obtained on a Micromass PlatformLC spectrophotometer. Elemental analyses were performed by Robertson Labs and are within 0.4% of theoretical values unless otherwise indicated. Column chromatography was performed on silica gel 60, 230−400 mesh, purchased from Mallinckrodt. Solutions were dried over magnesium sulfate. Yields are of purified product (except where noted), and reaction conditions were not optimized.

Preparation of Starting Materials. (5-Bromo-thiophen-2-yl)-methanol. A solution of 5-bromo-2-thiophenecarbaldehyde (26.2 g, 137 mmol) in MeOH (500 mL) was treated with $NaBH_4$ (5.2 g, 137 mmol). The reaction was stirred for 2 h at 0 °C and 2 h at room temperature. The MeOH was evaporated, and saturated NH_4Cl was added followed by 2 N HCl. The aqueous layers were extracted with EtOAc, dried, and concentrated. Flash chromatography using 100% CH_2Cl_2 as eluent afforded 23.3 g (92%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 4.74 (d, 2 H), 6.75 (m, 1 H), 6.91 (d, 1 H).

(3-Bromo-thiophen-2-yl)-methanol. A mixture of 3-bromothiophene-2-carboxylic acid methyl ester (9.9 g, 45 mmol), LAH (1.7 g, 45 mmol), and THF (150 mL) was stirred at 0 °C for 1 h and then overnight at room temperature. The reaction was worked up by addition of 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of H_2O followed by filtration through Celite. Concentration of the filtrate gave 6.5 g (75%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 4.80 (s, 2 H), 6.96 (d, 1 H), 7.26 (d, 1 H).

2-Methyl-thiazole-4-carbaldehyde. A mixture of 5.52 g (30 mmol) of 4-chloromethyl-2-methylthiazole hydrochloride and 0.5 M NaOH (180 mL) was refluxed for 8 h and then stirred for 18 h at room temperature. EtOAc and H_2O were added. The organic phase was separated, washed with brine, and dried. Concentration gave 2.2 g (57%) of 4-(hydroxymethyl)-2-methylthiazole which was clean enough to carry on

without purification. Yield: 2.2 g (57%). ^{1}H NMR ($CDCl_3$): δ 2.63 (s, 3 H), 4.66 (s, 2 H), 6.96 (s, 1 H). The crude product (2.2 g, 17 mmol) was oxidized with MnO_2 (20 g) in 75 mL of $CHCl_3$ for 16 h. The suspension was filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with 2:1 hexane:EtOAc, to give 1.4 g (36% over two steps) of the title compound as an oil which solidified upon standing. ^{1}H NMR ($CDCl_3$): δ 2.71 (s, 3 H), 7.98 (s, 1 H), 9.89 (s, 1 H).

5-Methyl-thiazole-4-carbaldehyde. A solution of 2.48 g (14.4 mmol) of 5-methyl-thiazole-4-carboxylic acid ethyl ester[19] in CH_2Cl_2 (50 mL) was cooled to −78 °C under nitrogen. DIBAL (1.0 M in CH_2Cl_2, 15 mmol) was added dropwise, and the solution was stirred at low temperature for 45 min. Another 10 mmol of DIBAL was then added dropwise, and the mixture was stirred for another 45 min. A solution of MeOH:CH_3CO_2H (10 mL:5 mL) was added slowly, followed by H_2O. The organic layer was separated, washed with brine, and dried. Concentration gave a residue which was chromatographed, eluting with 2:1 hexane:EtOAc, to give 1.02 g (56%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 2.76 (s, 3 H), 8.58 (s, 1 H), 10.14 (s, 1 H).

4-Isopropyl-thiazole-2-carbaldehyde. The title compound was prepared from 2.1 g (11 mmol) of 4-isopropyl-thiazole-2-carboxylic acid ethyl ester[20] and DIBAL (a total of 19 mmol of 1.0 M in CH_2Cl_2) in a fashion similar to the preparation of 5-methyl-thiazole-4-carbaldehyde. Chromatography of the crude product, eluting with 3:1 hexane:EtOAc, gave the title compound in 51% yield. ^{1}H NMR ($CDCl_3$): δ 1.35 (d, 6 H), 3.16−3.23 (m, 1 H), 7.33 (s, 1 H), 9.96 (s, 1 H).

2-Isopropyl-thiazole-4-carbaldehyde. The title compound was prepared from 2.7 g (13 mmol) of 2-isopropyl-thiazole-4-carboxylic acid ethyl ester[20] and DIBAL (a total of 30 mmol of 1.0 M in CH_2Cl_2) in a fashion similar to the preparation of 5-methyl-thiazole-4-carbaldehyde. Chromatography of the crude product, eluting with 3:1 hexane:EtOAc, gave 1.45 g (69%) of the title compound as a clear colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.37 (d, 6 H), 3.30−3.35 (m, 1 H), 8.01 (s, 1 H), 9.93 (s, 1 H).

5-Isopropyl-thiazole-4-carbaldehyde. The title compound was prepared from 6.8 g (37 mmol) of 5-isopropyl-thiazole-4-carboxylic acid methyl ester[19] in CH_2Cl_2 (120 mL) and DIBAL (a total of 57 mmol of 1.0 M in CH_2Cl_2) in a fashion similar to the preparation of 5-methyl-thiazole-4-carbaldehyde. Chromatography of the crude product, eluting with 2:1 hexane:EtOAc, gave 4.65 g (81%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 6 H), 4.09−4.16 (m, 1 H), 8.63 (s, 1 H), 10.20 (s, 1 H).

4-Isopropyl-thiazole-5-carbaldehyde. A solution of 5.9 g (30 mmol) of 4-isopropyl-thiazole-5-carboxylic acid ethyl ester[19] in toluene (100 mL) was cooled in an ice bath under nitrogen and treated dropwise with DIBAL (150 mL of 1.0 M; 150 mmol). The mixture was stirred at low temperature for 45 min and then allowed to warm to room temperature overnight. H_2O was added cautiously, and the mixture was extracted with EtOAc (3 × 200 mL). The combined extracts were washed with brine, dried, and concentrated. The crude 5-(hydroxymethyl)-4-isopropyl-thiazole thus obtained was used as is in the next step. ^{1}H NMR ($CDCl_3$): δ 1.30 (d, 6 H), 3.13−3.20 (m, 1 H), 4.85 (s, 2 H), 8.67 (s, 1 H).

A mixture of 4.65 g (30 mmol) of crude 5-(hydroxymethyl)-4-isopropyl-thiazole in 200 mL of $CDCl_3$ was treated with 45 g of MnO_2 and stirred at room temperature for 2.5 h. The suspension was filtered, and the filtrate was concentrated. The residue was chromatographed, eluting with 3:1 hexane:EtOAc, to give 2.35 g (51% over 2 steps) of the title compound. ^{1}H NMR ($CDCl_3$): δ 1.40 (d, 6 H), 3.62−3.69 (m, 1 H), 8.97 (s, 1 H), 10.17 (s, 1H).

Preparation of Ketones. General Method A. Synthesis of 4-Methyl-1-(4-methyl-thiazol-2-yl)-pentan-3-one (B-25). A mixture of 2.0 g (16 mmol) of 4-methyl-thiazole-2-carbaldehyde,[24] 8.9 g (19 mmol) of 3-methyl-2-oxobutyltriphenylarsonium bromide,[13] 2.6 g (19 mmol) of K_2CO_3, and 1% H_2O in CH_3CN was stirred for 18 h at room temperature. The solids were filtered, and the filtrate was concentrated. The residue was taken up in EtOAc and filtered; the filtrate was chromatographed, eluting with 1:2 EtOAc:hexane, to give 4-methyl-1-(4-methyl-thiazol-2-yl)-pent-1-en-3-one (2.5 g, 81%). ^{1}H NMR ($CDCl_3$): δ 1.13 (d, J = 6.8. Hz, 6 H), 2.45 (s, 3 H), 2.82−2.89 (m, 1 H), 6.96 (s, 1 H), 7.01 (d, J = 16 Hz, 1 H), 7.57 (d, J = 16 Hz, 1 H).

The enone was then dissolved in THF (100 mL), treated with 0.4 g of 5%Pd/$BaSO_4$, and shaken in a hydrogen atmosphere of 32 psi for 26 h. The catalyst was filtered, and the filtrate was concentrated. The crude product was chromatographed, eluting with 2:1 hexane:EtOAc, to give 1.3 g (55%) of the title ketone. ^{1}H NMR ($CDCl_3$): δ 1.05 (d, J = 6.8. Hz, 6 H), 2.34 (s, 3 H), 2.55−2.62 (m, 1 H), 2.93 (t, J = 7.1 Hz, 2 H), 3.18 (t, J = 7.2 Hz, 2 H), 6.65 (s, 1 H).

Ketones **B-1**, **B-3**, **B-6**, **B-14**, **B-15**, **B-16**, **B-26**, **B-27**, **B-28**, **B-29**, **B-30**, **B-31**, **B-32**, **B-33**, **B-34**, **B-36**, **B-37**, and **B-38** were prepared in similar fashion from the appropriate starting aldehyde as listed in Table 1. The yields reported are over two steps, including condensation and subsequent catalytic reduction.

General Method B. Synthesis of 1-Furan-2-yl-4-methyl-pentan-3-one (B-10). To a reaction flask was added 2-furancarbaldehyde (11.3 g, 117 mmol), 3-methyl-2-butanone (10.1 g, 117 mmol), 95% EtOH (200 mL), and anhydrous $Ba(OH)_2$ (2.2 g). The reaction was heated at 80 °C for 3 h and stirred at room temperature overnight. The EtOH was evaporated, and the residue was partitioned between EtOAc and 1 N HCl. The combined organic extract was dried and concentrated; the crude product was purified by flash chromatography, eluting with 50:50 hexane:CH_2Cl_2, to give 1-furan-2-yl-4-methyl-pent-1-en-3-one (6.1 g, 32%). ^{1}H NMR ($CDCl_3$): δ 1.15 (d, J = 7.1 Hz, 6 H), 2.82−2.90 (m, 1 H), 6.45 (m, 1 H), 6.65 (m, 1 H), 6.72 (d, J = 14 Hz, 1 H), 7.40 (d, J = 14 Hz, 1 H), 7.52 (m, 1 H).

The titled compound was prepared from the reduction of the enone (1.0 g, 6.2 mmol) with $(Ph_3P)_3RhCl$ (0.1 g) in THF (50 mL) under hydrogenation conditions similar to those used in general method A. The crude product was chromatographed, eluting with 98:2 hexane:EtOAc, to give 0.83 g (82%; 26% over two steps) of the title ketone. ^{1}H NMR ($CDCl_3$): δ 1.09 (d, J = 7.1 Hz, 6 H), 2.57−2.64 (m, 1 H), 2.80 (m, 2 H), 2.85 (m, 2 H), 5.99 (m, 1 H), 6.26 (m, 2 H), 7.28(m, 1 H).

General Method C. Synthesis of 4-Methyl-l-pyridin-3-yl-pentan-3-one (B-2). 3-Iodo-pyridine (7.50 g, 36.6 mmol), 4-methyl-1-penten-3-ol (5.45 g, 54.9 mmol), tetrabutylammonium chloride (10.2 g, 36.6 mmol), $NaHCO_3$ (6.15 g, 73.2 mmol), pyrrolidine (2 mL), DMF (25 mL), and $Pd(OAc)_2$ (0.01 equiv) were added to a reaction vessel.[14] The solution was heated to 80 °C for 18 h and then cooled to room temperature. The mixture was diluted with H_2O and CH_2Cl_2 and filtered through Celite. The organic extract was washed with brine, dried, and concentrated. The title compound was flash chromatographed, eluting with 98:2 CH_2Cl_2:MeOH, to give 5.15 g (79%) of the title ketone. ^{1}H NMR ($CDCl_3$): δ 1.15 (d, 6 H), 2.5−2.7 (m, 1 H), 2.7−2.9 (m, 2 H), 2.85−2.95 (m, 2 H), 7.2−7.3 (m, 1 H), 7.5−7.6 (m, 1 H), 8.4−8.5 (m, 2 H).

Similar procedures were used to prepare ketones **B-4**, **B-5**, **B-8**, and **B-9** from the corresponding bromides; the results are summarized in Table 1.

General Method D. Synthesis of 4-Methyl-1-thiophen-2-yl-pentan-3-one (B-12). A solution of 2-bromothiophene (14.7 g, 100 mmol), 4-methyl-1-penten-3-ol (15.0 g, 150 mmol), NaI (0.52 g, 3.5 mmol), $NaHCO_3$ (10.1 g, 120 mmol), PPh_3 (0.78 g, 3.0 mmol), $Pd(OAc)_2$ (0.22 g, 1.0 mmol), and DMF (0.1−1 mL per mmol of halide) was heated to 130 °C for 20 h.[14] The reaction was cooled to room temperature and partitioned between H_2O and ether. The organic extract was washed with brine, dried, and concentrated. The residue was chromatographed, eluting with hexane:EtOAc 95:5, to give 4.3 g (24%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 1.09 (d, 6 H), 2.54−2.64 (m, 1 H), 2.83 (t, J = 7.4 Hz, 2 H), 3.11 (t, J = 7.4 Hz, 2 H), 6.79 (m, 1 H), 6.88−6.92 (m, 1 H), 7.11 (m, 1 H).

Ketones **B-13**, **B-17**, **B-18**, **B-19**, **B-21**, and **B-23** were synthesized in a similar fashion from the appropriate halide, and the results are summarized in Table 1.

General Method E. Silylation of Intermediate Hydroxymethyl Ketones. Synthesis of 1-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-thiophen-2-yl]-4-methyl-pentan-3-one (B-20). A mixture of **B-19** (19.5 g, 73.0 mmol) in CH_2Cl_2 (300 mL) was treated with imidazole (5.47 g, 80.3 mmol) and cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (12.1 g, 80.3 mmol) was added, and the cold bath was removed. The reaction mixture was stirred at room temperature for 6 h. The suspension was filtered; the filtrate was washed with brine, dried, and concentrated. The product was flash chromatographed, eluting with hexane:EtOAc 95:5 to 92.5:7.5, to give 16.1 g (68%) of the title compound. ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 6 H), 0.92 (s, 9 H), 1.09 (d, 6 H), 2.59 (m, 1 H), 2.81 (t, 2 H), 3.06 (t, 2 H), 4.78 (s, 2 H), 6.61 (d, 1 H), 6.69 (d, 1 H).

Silylated intermediates **B-22** and **B-24** were prepared from compounds **B-21** and **B-23**, respectively, in a similar fashion. In these examples, the final product was not purified but used crude in the next step.

4-Methyl-1-(1-trityl-1*H*-pyrazol-3-yl)-pentan-3-one (B-7). Compound **B-6** (1.96 g, 12 mmol) was dissolved in DMF (10 mL) and treated with trityl chloride (3.3 g, 12 mmol). The mixture was stirred for 5 min, treated with NEt_3, and stirred overnight at room temperature. The solution was poured into water and extracted with ether; the organic phase was dried and concentrated. Chromatography of the residue, eluting with 9:1 hexane:EtOAc, gave 4.8 g (99%) of the title compound.

4-Methyl-1-(tetrahydro-furan-2-yl)-pentan-3-one (B-11). A mixture of **B-10** (1.14 g, 7.00 mmol), 5% $Pd/CaCO_3$ (0.2 g), and THF (100 mL) was shaken in a hydrogen atmosphere of 42 psi at 25 °C for 1.5 h. At that time, 20% Pd/C (0.4 g) was added, and the reaction mixture was shaken in a hydrogen atmosphere for another 50 h. The catalysts were filtered, and the filtrate was concentrated. Chromatography of the residue, eluting with 99:1 CH_2Cl_2:MeOH, yielded 0.88 g (74%) of the title compound as a mixture of stereoisomers. ^{1}H NMR ($CDCl_3$): δ 1.10 (d, J = 6.8 Hz, 6 H), 1.46−2.04 (m, 6 H), 2.47−2.66 (m, 3 H), 3.67−3.75 (m, 1 H), 3.77−3.87 (m, 2 H).

2,2,2-Trifluoro-*N*-[4-(4-methyl-3-oxo-pentyl)-thiazol-2-yl]-acetamide (B-35). A solution of **B-34** (1.21 g, 5.03 mmol) in 6 N HCl (50 mL) and THF (5 mL) was refluxed for 4 h and then cooled to room temperature. Solid $NaHCO_3$ was added portionwise with caution until pH 7.2 was achieved. The suspension was extracted with EtOAc. The combined extracts were washed with brine, dried, and concentrated. The residue was chromatographed, eluting with EtOAc, to give the deprotected intermediate. ^{1}H NMR ($CDCl_3$): δ 1.04 (d, 6 H), 2.52−2.59 (m, 1 H), 2.75 (m, 4 H), 6.06 (s, 1 H).

A solution of the ketone prepared above (0.75 g, 3.8 mmol) in CH_2Cl_2 (50 mL) was cooled in an ice bath, treated with NEt_3 (0.6 mL, 4.3 mmol) and trifluoromethyl acetic anhydride (0.6 mL, 4.3 mmol), and allowed to warm to room temperature. H_2O was added. The organic layer was separated, washed with brine, and dried. Concentration gave an oil which was chromatographed over silica gel, eluting with EtOAc, to give 0.70 g (55% over two steps) of the title compound. ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 6 H), 2.58−2.65 (m, 1 H), 2.83−2.86 (m, 2 H), 2.91−2.95 (m, 2 H), 6.61 (s, 1 H).

General Method for the Preparation of 4-Hydroxy-5,6-dihydropyrones. 4-Hydroxy-6-isopropyl-6-[2-(4-methyl-thiazol-5-yl)-ethyl]-5,6-dihydro-pyran-2-one (D-25). Methyl acetoacetate (1.00 g, 8.61 mmol) was added dropwise to a slurry of NaH (0.38 g, 9.5 mmol) in 100 mL of anhydrous THF at 0 °C, and the mixture was stirred at 0 °C for 20 min. *n*-Butyllithium (4.5 mL of 2.1 M; 9.45 mmol) was then added, and the reaction mixture was stirred at 0 °C for 30 min. A solution of **B-29** (1.53 g, 142 mmol) in THF (50 mL) was added all at once. The solution was stirred at 0 °C to room temperature for 90 min, then treated with 0.1 N HCl with stirring. The THF was evaporated; the residue was partitioned between H_2O and EtOAc. The organic layer was separated, dried, and concentrated. The crude aldol product was dissolved in 20 mL of THF, treated with 200 mL of 1.0 N NaOH, and stirred for 1 h. The solution was washed with Et_2O. The aqueous phase was cooled in an ice bath, acidified to pH 4.5 with 1.0 N HCl, and extracted with EtOAc. The extract was washed with brine, dried, and concentrated. Chromatography of this residue, eluting with 95:5 CH_2Cl_2:MeOH, gave 1.57 g (72%) of the title compound. ^{1}H NMR (DMSO-d_6): δ 0.87−0.90 (m, 6 H), 1.82−1.96 (m, 2 H), 2.07−2.18 (m, 1 H), 2.25 (s, 3 H), 2.31 (d of ABX q, J = 17.8 Hz, 1 H), 2.60 (d of ABX q, J = 18 Hz, 1 H), 2.74−2.81 (m, 2 H), 4.96 (s, 1 H), 8.78 (s, 1 H), 11.39 (s, 1 H). MS (APCI): $AP^+ = 282$.

Compounds **D(1−6)**, **D(8−17)**, and **D(21−34)** were prepared in the same fashion from the analogous ketones. The results are summarized in Table 2. During the workup of the pyrazole analogue, the trityl protecting group was inadvertently cleaved to give the free pyrazole **D-7** in Table 2. For compounds **D**(**18−20**), a slightly modified procedure was used as follows: The crude aldol product isolated after the first step was dissolved in THF and treated with Bu_4NF (1.5 equiv) The reaction mixture was stirred at room temperature for 3 h, then concentrated, and dissolved in Et_2O. The solution was washed with dilute HCl, dried, and concentrated. This material was then dissolved in THF, diluted with 1.0 N NaOH, and stirred for 1 to 3 h. The reaction mixture was worked up as before to give the desired compounds.

General Method for the Preparation of Final Dihydropyrones. 3-(2-*tert*-Butyl-4-hydroxymethyl-5-methyl-phenylsulfanyl)-4-hydroxy-6-isopropyl-6-[2-(4-methyl-thiazol-5-yl)-ethyl]-5,6-dihydro-pyran-2-one (26). A mixture of **D-25** (0.22 g, 0.78 mmol) in DMF (4 mL) was treated with toluene-4-thiosulfonic acid *S*-(2-*tert*-butyl-4-hydroxymethyl-5-methyl-phenyl) ester (0.33 g, 0.90 mmol) and K_2CO_3 (1.0 g, 7.2 mmol). The suspension was stirred overnight at room temperature and then poured into a mixture of EtOAc and either 1 N HCl or saturated NH_4Cl. The organic phase was separated, washed with brine, dried and concentrated. Chromatography (10% MeOH in CH_2Cl_2) afforded the title compound, mp 138−141 °C. ^{1}H NMR (DMSO-d_6): δ 0.90−0.96 (m, 6 H), 1.46 (s, 9 H), 1.85 (s, 3 H), 1.95−2.00 (m, 2 H), 2.15−2.23 (m, 4 H), 2.70−2.82 (m, 3 H), 2.93 (d of ABX q, 1 H), 4.34 (s, 2 H), 4.92 (br s, 1 H), 6.66 (s, 1 H), 7.24 (s, 1 H), 8.79 (s, 1 H).

Compounds **1**−**31** and **33**−**36** were prepared in similar fashion from the thiotosylate and the dihydropyrone from Table 2. For compound **32**, the thiotosylate was reacted with the trifluroacetamide **D-33** under the general conditions listed above, and the protecting group was removed using dilute NaOH. For compound **8**, the thiotosylate was reacted with the trityl-protected compound **D-6** under the same general conditions, and the protecting group was removed with acetic acid in methanol.

Preparation of Chiral Dihydropyrones. Preparation of β-Hydroxyester from Ketone B-13. Diisopropylamine (43 mmol) was cooled to −10 °C and treated with *n*BuLi (43 mmol) over 20 min. The solution was stirred for 30 min at −10 °C and then cooled to −78 °C. *tert*-Butyl acetate (42.6 mmol) was dissolved in THF and added dropwise to the LDA solution over 30 min. When addition was complete, the reaction mixture was stirred at −78 °C to −40 °C for another 60 min. A solution of ketone **B-13** (21 mmol) in THF was added over 15 min, and the reaction mixture was warmed to room temperature. The solution was poured into 1 N HCl and ice; the product was extracted into EtOAc, dried, and concentrated. Purification via chromatography, eluting with hexane:EtOAc 97:3, afforded the title compound as the *tert*-butyl ester. ^{1}H NMR ($CDCl_3$): δ 0.95 (dd, 6 H), 1.47 (s, 9 H), 1.7−2.0 (m, 3 H), 2.36−2.54 (AB q, 2 H), 2.6−2.8 (m, 2 H), 6.93−6.95 (m, 2 H), 7.23−7.25 (m, 1 H).

Separation of β-Hydroxy Ester Enantiomers via Chiral HPLC: (*S*)-3-Hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic Acid *tert*-Butyl Ester (E-(*S*)). The title compound was prepared by resolution on a Chiralpak AD column eluting with 1:99 2-propanol:hexane to afford both enantiomers of 3-hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic acid *tert*-butyl ester. The *S* enantiomer eluted first. ^{1}H NMR ($CDCl_3$): δ 0.95 (dd, 6 H), 1.47 (s, 9 H), 1.7−2.00 (m, 3 H),

2.36−2.54 (AB q, 2 H), 2.6−2.8 (m, 2 H), 6.93−6.95 (m, 2 H), 7.23−7.25 (m, I H).

(*R*)-3-Hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic Acid *tert*-Butyl Ester (E-(*R*)). The *R* enantiomer eluted second: ^{1}H NMR ($CDCl_3$): δ 0.95 (dd, 6 H), 1.47 (s, 9 H), 1.7−2.00 (m, 3 H), 2.36−2.54 (AB q, 2 H), 2.6−2.8 (m, 2 H), 6.93−6.95 (m, 2 H), 7.23−7.25 (m, 1 H).

(*S*)-3-Hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic Acid (F-(*S*)). Ester (*S*)-3-hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic acid *tert*-butyl ester (8 mmol) was dissolved in EtOH and treated with LiOH (16 mmol), H_2O (5 mL), and MeOH (15 mL). The mixture was stirred at room temperature for 18 h and concentrated. The residue was partitioned between H_2O and Et_2O. The aqueous layer was separated, acidified with 1 N HCl, and extracted with Et_2O. The solution was dried and concentrated to give the title compound: ^{1}H NMR ($CDCl_3$): δ 0.98 (t, 6 H), 1.8−2.0 (m, 3 H), 2.50−2.70 (AB q, 2 H), 2.6−2.8 (m, 2 H), 6.93−6.95 (m, 2 H), 7.23−7.25 (m, 1 H).

The *R* isomer was prepared in identical fashion from the *R* ester.

Preparation of the Chiral β-Ketoester from β-Hydroxy Acid: (*S*)-5-Hydroxy-6-methyl-3-oxo-5-(2-thiophen-3-yl-ethyl)-heptanoic Acid Ethyl Ester (G-(*S*)). A solution of (*S*)-3-hydroxy-4-methyl-3-(2-thiophen-3-yl-ethyl)-pentanoic acid (7.81 mmol) as isolated above in THF (30 mL) was treated with CDI (8.6 mmol) and stirred for 18 h at room temperature. Bis [3-methoxy-3-oxopropanoato (1-)-O,O′] magnesate (15.6 mmol) was added, and the reaction was stirred for 6 h at room temperature. The reaction was concentrated and the residue partitioned between EtOAc and 1 N HCl. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried, and concentrated. Purification was accomplished using silica gel chromatography, eluting with 100% CH_2Cl_2: ^{1}H NMR ($CDCl_3$): δ 0.94 (dd, 6 H), 1.27 (t, 3 H), 1.75−1.90 (m, 2 H), 1.9−2.0 (m, 1 H), 2.65−2.75 (m, 3 H), 2.80 (d, 1 H), 3.48 (s, 2 H), 4.15−4.25 (m, 2 H), 6.93 (m, 2 H), 7.2−7.3 (m, 1 H).

The *R* isomer was prepared in identical fashion from the *R* acid.

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