Structure−Activity Relationships for Inhibition of Inosine Monophosphate Dehydrogenase by Nuclear Variants of Mycophenolic Acid[1]

Peter H. Nelson,[†] Stephen F. Carr,[‡] Bruce H. Devens,[§] Elsie M. Eugui,[§] Fidencio Franco,[∥] Carlos Gonzalez,[∥] Ronald C. Hawley,[†] David G. Loughhead,*[,†] David J. Milan,[†] Eva Papp,[‡] John W. Patterson,[†] Sussan Rouhafza,[§] Eric B. Sjogren,[†] David B. Smith,[†] Rebecca A. Stephenson,[†] Francisco X. Talamas,[∥] Ann-Marie Waltos,[†] Robert J. Weikert,[†] and John C. Wu[‡]

Institutes of Organic Chemistry, Immunology and Biological Sciences, and Biochemistry and Cell Biology, Syntex Research, 3401 Hillview Avenue, Palo Alto, California 94304

Received May 20, 1996[⊗]

Structure−activity relationships in the region of the phthalide ring of the inosine monophosphate dehydrogenase inhibitor mycophenolic acid have been explored. Replacement of the lactone ring with other cyclic moieties resulted in loss of potency, especially for larger groups. Replacement of the ring by acyclic substituents also indicated a strong sensitivity to steric bulk. A phenolic hydroxyl group, with an adjacent hydrogen bond acceptor, was found to be essential for high potency. The aromatic methyl group was essential for activity; the methoxyl group could be replaced by ethyl to give a compound with 2−4 times the potency of mycophenolic acid in vitro and in vivo.

Mycophenolic acid (MPA) (**1a**) is produced by fermentation of several penicillium species.[2] It has diverse in vitro and in vivo biological activities, including antifungal,[3] antibacterial,[4] antiviral,[5] and immunosuppressive[6] properties. Mycophenolic acid itself has been tested clinically against various tumors without success[7] and has been found to be effective as an antipsoriatic.[8] The compound is an inhibitor of inosine-5′-monophosphate dehydrogenase (IMPDH, EC 1.1.1.205), and this inhibition is believed to mediate the above-described biological properties.[9] IMPDH catalyzes the NAD-dependent conversion of inosine-5′-phosphate to xanthosine-5′-phosphate and is thus a key enzyme in the de novo synthesis of guanine nucleotides. IMPDH exists in type I and type II isoforms;[10] the type II isoform is selectively upregulated during cell proliferation.[11] Since, unlike many other cell types, lymphocytes are dependent on de novo purine biosynthesis,[12] inhibitors of IMPDH would be expected to be immunosuppressive without exhibiting general cytotoxicity. Thus we have sought MPA analogs or derivatives with high IMPDH inhibitory potency for the potential therapy of autoimmune diseases and for the prevention of allograft rejection. Mycophenolate Mofetil (RS-61443),[13] a prodrug of MPA, has been found to be clinically effective in rheumatoid arthritis[14] and, following clinical trials for the reversal and prevention of kidney and heart transplant rejection,[15] was approved in the United States in 1995 for use by renal transplant patients.

We have previously attempted to increase the inhibitory potency of mycophenolic acid against IMPDH by modification of the side-chain moiety, particularly by replacement of the double bond by other groups.[16] Inhibitory potency was found to be very sensitive to small changes in the side-chain structure. In the present paper we report on structure−activity relationships (SAR) associated with changes in the nucleus of MPA. The goal of the work has been to identify compounds with increased in vitro and in vivo immunosuppressive potency, preferably with simpler structures more amenable to total synthesis than MPA itself. We have also prepared compounds designed to increase the in vivo potency by alteration of the metabolism. Although MPA has an IC_{50} of ca. 20 nM against IMPDH, effective immunosuppressive doses in both animals[17] and man[7] are in the range of 10−100 mg/kg. MPA is well absorbed after oral administration, but it is rapidly converted into the biologically inactive phenolic glucuronide in several species which have been examined, including man,[18] and subsequently excreted as such. Since removal of this mode of inactivation and excretion might result in compounds with higher in vivo potencies, we have prepared a number of compounds in which the phenolic hydroxyl has been replaced by groups not susceptible to glucuronidation. Other workers have described a limited number of MPA analogs in which the phthalide nucleus has been either replaced or modified, though often without biological data.[19] The somewhat fragmentary published data suggest that changes in the nucleus, as in the side chain, result in considerable loss of potency.

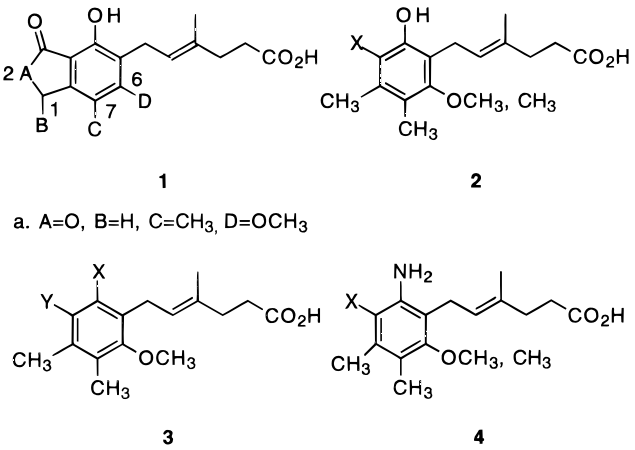
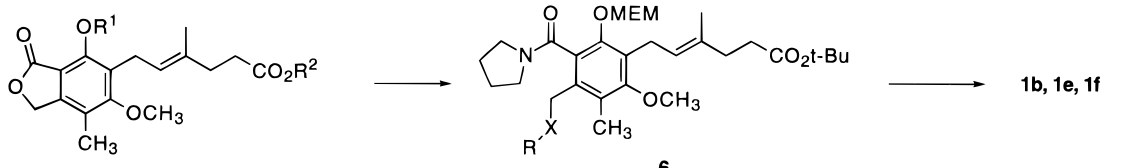


Figure 1.

* Send correspondence to this author at Roche Bioscience, 3401 Hillview Ave., Palo Alto, CA 94304.
[†] Institute of Organic Chemistry.
[‡] Institute of Biochemistry and Cell Biology.
[§] Institute of Immunology and Biological Sciences.
[∥] División de Investigación, Syntex S.A. de C.V., Cuernavaca, México.
[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1996.

S0022-2623(96)00363-9 CCC: $12.00

Scheme 1



5

a. R^1=MEM, R^2=t-Bu

b. R^1=TBS, R^2=Me

6

a. R=H, X=O

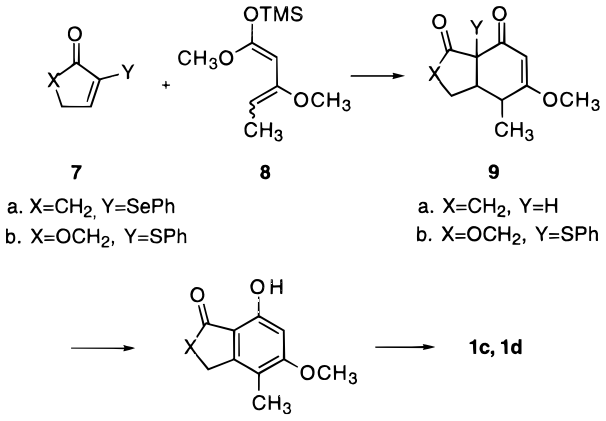
b. R=CH_3SO_2, X=O

c. R=Ac, X=S

d. RX=N_3

1b, 1e, 1f

Scheme 2



7

a. X=CH_2, Y=SePh

b. X=OCH_2, Y=SPh

8

9

a. X=CH_2, Y=H

b. X=OCH_2, Y=SPh

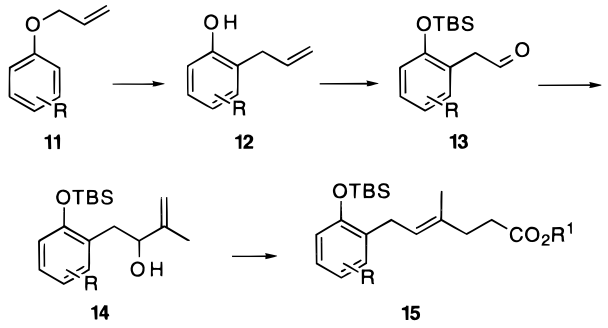
10

a. X=CH_2

b. X=OCH_2

1c, 1d

Scheme 3



11

12

13

14

15

Chemistry

The compounds synthesized can be divided into four groups: structures **1**, in which the lactone ring has been replaced by other cyclic moieties or in which the aromatic 6-methoxy and 7-methyl groups have been varied; monocyclic phenols **2**; monocyclic non-phenols **3**; and monocyclic amines **4**. The majority of the analogs were made by total synthesis and some by degradation/modification of mycophenolic acid. The bicyclic compounds **1** were made by both approaches: Trimethylaluminum-mediated aminolysis of the protected MPA derivative **5a** gave the ring-opened benzyl alcohol intermediate **6a** (Scheme 1). Conversion of the alcohol to the mesylate **6b**, followed by displacement with nucleophiles, then allowed construction of the new heterocycles **1b,e,f** (Table 1).

Alternatively, modified nuclei were made by Diels–Alder reactions (Scheme 2) to afford the dihydroaromatic products **9**, which were aromatized to the phenols **10**. The side chain was then introduced by a previously published route, in which the critical step is conversion of the allylic carbinol **14** to esters **15** using the ortho-ester Claisen rearrangement (Scheme 3).[20] Most of the 6-substituted compounds **1h–q** were made from differentially protected intermediates such as **16d** (Scheme 4), from which the triflate group could be displaced by nucleophiles or replaced by coupling with organostannanes under palladium catalysis to introduce carbon substituents (vinyl, cyclopropyl, phenyl). The 6-methyl (**1m**) and 7-ethyl (**1s**) analogs were made by total syntheses (Schemes 5 and 6). Two of the 7-substituted products (**1v**,**w**) were prepared from the ester of 7-bromo compound **1t** (Scheme 7). Synthesis of most of the monocyclic phenols **2** was achieved by preparation of the appropriately substituted phenolic precursor and then attachment of the side chain as in Scheme 3. Other compounds of this type were made from MPA, which upon prolonged treatment with strong aqueous base afforded the decarboxylated product **27a** (Scheme 8). Following reductive deoxygenation to give **2a**, various substituents X (Table 2) were introduced.

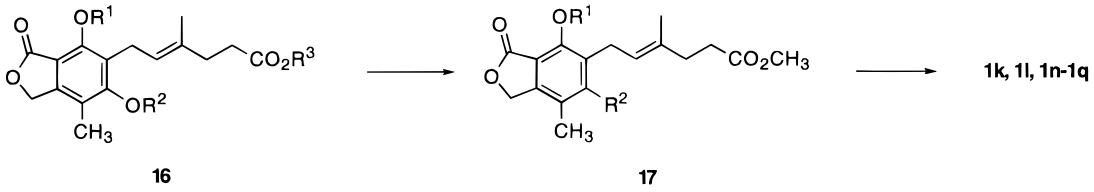
The non-phenols **3a–s** were synthesized analogously to Scheme 3, except that the phenolic oxygen atom in the Claisen product (**12**) became part of the methoxyl group in the final product. For the amines **4**, another variant of the ortho-ester Claisen methodology, shown in Scheme 9, was employed. In this route, the side chain was derived from an *o*-methylaniline (**28**). Conversion to the *t*-BOC derivative **29** facilitated metalation with *tert*-butyllithium,[21] and reaction of the resultant benzylic anion with methacrolein then afforded the carbinols **30** which underwent ortho-ester Claisen rearrangement to give the products **31**.

Biological Results

Compounds were tested as inhibitors of human recombinant type II IMPDH.[22] Results (Tables 1–4) are expressed as micromolar IC_{50} concentrations. Most of the compounds were also assayed as inhibitors of mitogen-induced human peripheral lymphocyte proliferation,[16] an assay which is an in vitro model for in vivo immunosuppression but independent of absorption, metabolism, and excretion parameters which affect in vivo potencies. In general, results from the two assays correlate, although potencies in the cell proliferation assay were always somewhat lower than for enzyme inhibition. A number of the more potent compounds were also tested in vivo for immunosuppressant activity.

The bicyclic analogs **1b–g** were all less potent inhibitors of IMPDH than the parent **1a**. Replacement of the

Scheme 4



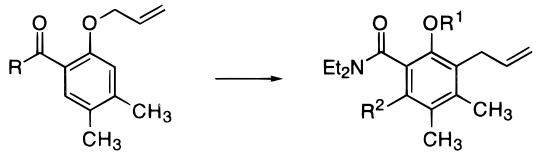
16

	R^1	R^2	R^3
a.	SO_2CF_3	SO_2CF_3	CH_3
b.	H	SO_2CF_3	CH_3
c.	MEM	SO_2CF_3	CH_3
d.	Ts	SO_2CF_3	CH_3
e.	H	CH_3	CH_3
f.	Ts	CH_3	CH_3
g.	Ts	H	H
h.	Ts	H	CH_3

17

	R^1	R^2
a.	MEM	H
b.	Ts	$CH=CH_2$
c.	Ts	CH_2CH_3
d.	Ts	cyclopropyl
e.	Ts	Ph
f.	H	CN

Scheme 5

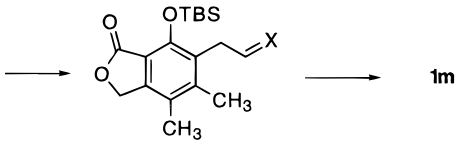


18

a. R=OCH_3
b. R=NEt_2

19

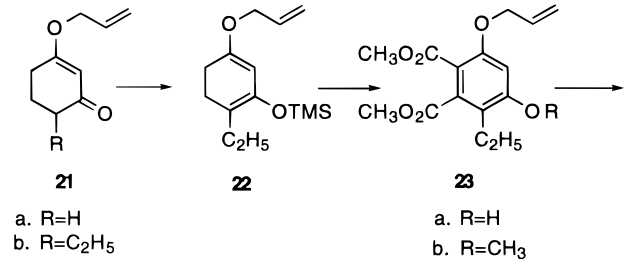
	R^1	R^2
a.	H	H
b.	TBS	H
c.	TBS	CHO
d.	TBS	CH_2OH



20

a. $X=CH_2$
b. X=O

Scheme 6



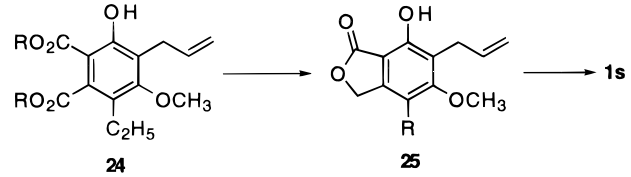
21

a. R=H
b. $R=C_2H_5$

22

23

a. R=H
b. $R=CH_3$



24

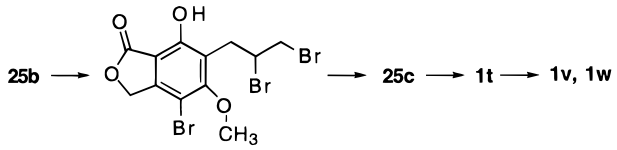
a. $R=CH_3$
b. R=H

25

a. $R=C_2H_5$
b. R=H
c. R=Br

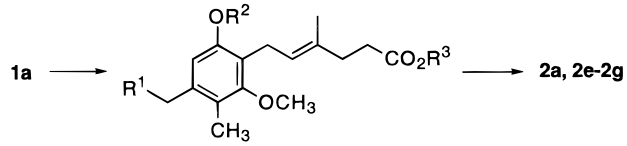
lactone oxygen with sulfur (**1b**), CH_2 (**1c**), or NH (**1e**) resulted in a 5−10-fold reduction in potency. Replacement with the larger NCH_3 group gave a compound (**1f**)

Scheme 7



26

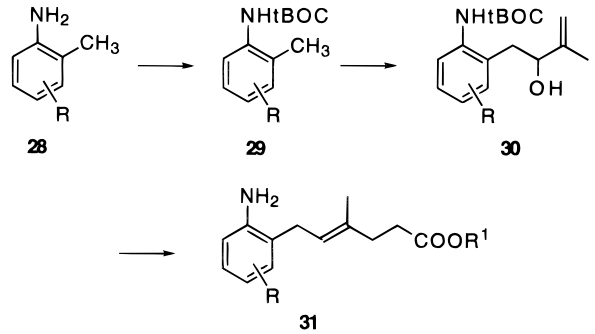
Scheme 8



27

	R^1	R^2	R^3
a.	OH	H	H
b.	OH	H	CH_3
c.	OH	Ac	CH_3
d.	AcS	Ac	CH_3
e.	H	Ac	CH_3
f.	H	H	CH_3

Scheme 9



28

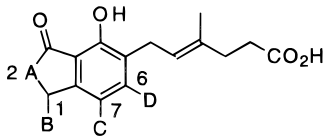
29

30

31

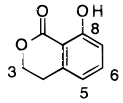
which was more than 400-fold less potent than the NH compound **1e**, a result which suggests a strong sensitivity to steric bulk in this area of the molecule. The *N*-methyl group occupies a volume which is not explored in other analogs, and its low inhibitory potency suggests that it cannot be accommodated at the IMPDH active site. Increasing the size of the lactone ring in **1a** to 6 (**1d**) diminished the potency 25-fold. Addition of a methyl substituent to the phthalide methylene (**1g**) also resulted in a marked decrease in potency attributable to a steric effect. More encouraging results were

Table 1. Bicyclic Compounds



compd	A	B	C	D	IMPDH IC_{50} (μM)	ASE[a]	lc prolifn IC_{50} (μM)
1a	O	H	CH_3	OCH_3	0.0251[b] (31)[c] 0.0248[d] (50)	0.0092 0.00044	0.058 ± 0.003
1b	S	H	CH_3	OCH_3	0.121[d] (3)	0.069	1.7
1c	CH_2	H	CH_3	OCH_3	0.140[b]	0.042	0.62, 0.83
1d[e]	OCH_2	H	CH_3	OCH_3	0.644[d]	0.231	8.6
1e	NH	H	CH_3	OCH_3	0.244[d]	0.244	1.50
1f	NCH_3	H	CH_3	OCH_3	>100[d,f]		>10[f]
1g	O	CH_3	CH_3	OCH_3	0.420[d]	0.139	0.60
1h[g]	O	H	CH_3	OH	0.0877[d] (2)	0.0105	>10[f]
1i[g]	O	H	CH_3	OC_2H_5	0.0898[d] (2)	0.0273	0.43, 0.43
1j	O	H	CH_3	H	6.96[d]	0.624	NT
1k	O	H	CH_3	$CH{=}CH_2$	0.00851[b]	0.0036	0.093
1l	O	H	CH_3	C_2H_5	0.0126[b] (2)	0.0025	0.057, 0.028
1m	O	H	CH_3	CH_3	0.0186[d] (2)	0.0018	0.25, 0.11
1n	O	H	CH_3	cyclopropyl	0.0507[b]	0.0036	0.34
1o	O	H	CH_3	C_6H_5	0.130[b]	0.018	2.8
1p	O	H	CH_3	CN	15.5[b]	2.93	>10[f]
1q	O	H	CH_3	$CONH_2$	0.231[b]	0.043	>10[f]
1r	O	H	H	OCH_3	0.515[d]	0.137	NT
1s	O	H	C_2H_5	OCH_3	0.410[d]	0.050	3.0
1t	O	H	Br	OCH_3	0.975[d]	0.152	4.0
1u	O	H	OCH_3	OCH_3	0.126[d] (2)	0.0097	0.13
1v	O	H	CN	OCH_3	>100[d,f] (2)		>10[f]
1w	O	H	$CONH_2$	OCH_3	>100[d,f] (2)		>10[f]

[a] Asymptotic standard error for IC_{50}. [b] Measured at pH 7.4. [c] Number of determinations if >1. [d] Measured at pH 8.0. [e] Number system for compound **1d**:

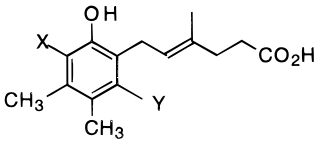


[f] Compounds were tested to 100 and 10 μM, respectively, in the IMPDH and lc prolifn assays. If no inhibition was observed, potency is designated as >100 and >10. Otherwise IC_{50} values are reported. [g] See ref 19b.

obtained by variations at the 6 (methoxyl)-position. Replacement of the methoxyl with vinyl, ethyl, or methyl (**1k**−**m**) gave products with equal or higher inhibitory potencies to MPA. Larger groups such as ethoxy (**1i**),[19b,23] cyclopropyl (**1n**), or phenyl (**1o**) or a smaller one such as hydrogen (**1j**) were much less potent. The 6-phenyl compound **1o** was less potent in the lymphocyte proliferation assay than would be expected from the IMPDH potency, an effect which may be due to less facile penetration through the cell membrane by this more lipophilic compound. The high potency of the 6-ethyl compound **1l** suggests that the 6-substituent does not interact with IMPDH by hydrogen bonding and, in view of the low potency of the 6-unsubstituted compound **1j**, suggests that a major function of the 6-substituent is to influence the orientation of the adjacent side chain. The lower potency of the 6-cyano (**1p**) and 6-carbamoyl (**1q**) compounds can be ascribed to the undesirability of dipolar character at this locus and/or to an unfavorable reduction in electron density at the lactone carbonyl group. Variations at the 7-position indicated that the methyl group present in MPA was the optimum. Larger (ethyl, **1s**; methoxyl, **1u**) or smaller (H, **1r**) groups resulted in a ca. 10−50-fold drop in potency. Electron-withdrawing substituents (CN, $CONH_2$) gave inactive compounds, either through a local effect on binding or due to increased acidity of the phenol moiety.

Since replacement of the lactone ring with significantly larger groups was not fruitful, we sought monocyclic replacements whose bulk would not be larger than the MPA phthalide. In most cases, the aromatic methyl and methoxyl groups present in MPA were retained so as to allow the effect of single structural changes to be assessed. The results for the monocyclic phenols (Table 2) also suggest sensitivity to steric bulk, though other factors are also relevant. Compounds **2a**−**l** differ only in the substituent adjacent to the phenolic hydroxyl group, yet the IMPDH inhibitory potencies range over more than 3 orders of magnitude. The unsubstituted phenol **2a** is of low potency; introduction of a methyl group into the ortho position (**2b**) results in a 60-fold increase. Yet isosteric[24] replacement of the methyl group with chloro (**2d**) causes a further 1 order of magnitude increase in potency, indicating a major effect not related to steric bulk. The chlorophenol **2d** is the most potent non-phthalide analog of MPA yet reported, showing 0.7 times the potency of MPA in inhibition of IMPDH. Rationalization of the significant differences in potency between the analogs is difficult, though some trends are discernible. Two criteria for high potency are that the substituent X can function as a hydrogen bond acceptor and it must be neither too large (iodo, **2f**) nor too small (fluoro, **2c**). Based on these criteria, the formyl-substituted compound **2i** was expected to be among the most potent analogs, yet it was about 30-fold less potent than the almost isosteric chloro compound **2d**. We hypothesize that the intramolecular H-bond in **2i** is strong enough to greatly diminish, relative to **1a**, participation by the phenol hydroxyl group in H-bond donation to the enzyme. Table 2 also contains some compounds in which the aromatic meth-

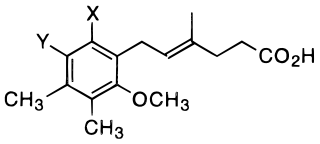
Table 2. Monocyclic Phenols



compd	X	Y	IMPDH IC_{50} (μM)[a]	ASE[b]	lc prolifn IC_{50} (μM)
1a	N/A	N/A	0.0248 (50)[c]	0.00044	0.058 ± 0.003
2a	H	OCH_3	51.8 (2)	68.0	NT
2b	CH_3	OCH_3	0.959 (2)	0.214	3.7
2c	F	OCH_3	1.08 (2)	0.114	4.1
2d	Cl	OCH_3	0.0335 (3)	0.0065	0.20, 0.33
2e	Br	OCH_3	0.0367 (3)	0.0384	0.28, 0.26
2f	I	OCH_3	0.592	0.119	4.9
2g	NO_2	OCH_3	0.184	0.083	NT
2h	CN	OCH_3	0.534	0.344	1.7
2i	CHO	OCH_3	1.12 (3)	0.789	10.0
2j	CH=NOH	OCH_3	11.9	1.27	>10[d]
2k	$CH=NOCH_3$	OCH_3	52.8	4.35	>10[d]
2l	CH_3O	OCH_3	11.9	1.27	NT
2m	H	CH_3	>100[d]		NT
2n	Cl	CH_3	0.0693	0.0087	0.36, 0.87
2o	Br	CH_3	0.620 (2)	0.174	1.65
2p	NO_2	CH_3	0.289	0.251	3.2

[a] Measured at pH 8.0. [b] Asymptotic standard error for IC_{50}. [c] Number of determinations if >1. [d] Compounds were tested to 100 and 10 μM, respectively, in the IMPDH and lc prolifn assays. If no inhibition was observed, potency is designated as >100 and >10. Otherwise IC_{50} values are reported.

Table 3. Non-phenols



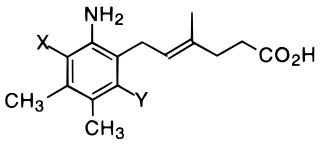
compd	X	Y	IMPDH IC_{50} (μM)[a]	ASE[b]	lc prolifn IC_{50} (μM)
1a	N/A	N/A	0.0248 (50)[c]	0.00044	0.058 ± 0.003
3a	H	Cl	0.537	0.371	6.7
3b	H	Br	0.795 (4)	0.192	>10[d]
3c	H	NO_2	1.22	0.136	9.5
3d	H	NH_2	17.0	1.11	NT
3e	H	OH	>100[d]		NT
3f	H	CH_3O	50.0	11.1	NT
3g	H	CN	1.60	0.366	NT
3h	H	CH_3S	52.3	3.62	>10[d]
3i	H	CH_3SO	>100[d]		>10[d]
3j	F	F	1.38	0.271	>10[d]
3k	Cl	F	11.8	1.20	>10[d]
3l	Cl	Cl	0.557	0.141	>10[d]
3m	F	Cl	0.437 (6)	0.208	7.5
3n	Cl	H	18.8	9.84	>10[d]
3o	Cl	NO_2	1.80	0.185	>10[d]
3p	Cl	OH	2.88	0.910	>10[d]
3q	Cl	CN	0.681	0.0837	>10[d]
3r	Cl	Br	1.04	0.357	>10[d]
3s	CH_3	Cl	1.70	0.957	>10[d]

[a] Measured at pH 8.0. [b] Asymptotic standard error for IC_{50}. [c] Number of determinations if >1. [d] Compounds were tested to 100 and 10 μM, respectively, in the IMPDH and lc prolifn assays. If no inhibition was observed, potency is designated as >100 and >10. Otherwise IC_{50} values are reported.

oxyl group has been replaced by methyl (**2m**−**p**). These compounds, which are more easily accessible, are 2-10-fold less potent than the methoxyl analogs. In contrast, replacement of the methoxyl group in MPA itself by methyl (**1m**) had no effect on inhibitory potency.

Replacement of the phenolic hydroxyl group with H resulted in a 3-20-fold decrease in potency, depending on the adjacent substituent (Table 3). Substituent effects among the non-phenols were less pronounced than for the phenols, however, and 10 compounds had

Table 4. Amino Compounds



compd	X	Y	IMPDH IC_{50} (μM)[a]	ASE[b]	lc prolifn IC_{50} (μM)
1a	N/A	N/A	0.0248 (50)[c]	0.00044	0.058 ± 0.003
4a	H	CH_3	90.8	414	NT
4b	Br	CH_3	0.763	0.089	NT
4c	Br	OCH_3	0.462 (3)	0.129	4.1, 2.3, 1.7
4d	NO_2	OCH_3	0.465	0.093	2.8
4e	CN	OCH_3	14.8	2.75	4.1
4f	Cl	OCH_3	0.489 (2)	0.236	4.1, 3.4, 1.4

[a] Measured at pH 8.0. [b] Asymptotic standard error for IC_{50}. [c] Number of determinations if >1.

comparable potencies of about 1 μM. As in previous series, larger substituents such as methoxyl (**3f**) and methylthio (**3h**) or smaller ones such as H (**3n**) or F (**3k**) were not tolerated in the Y position. With a chloro at Y, compounds of about equal potency were obtained by replacing the hydroxyl with H (**3a**), F (**3m**), Cl (**3l**), or CH_3 (**3s**). In the phenol series, Cl (**2d**) and CH_3 (**2b**) were greatly superior to F (**2c**) and H (**2a**) as adjacent substituents. Thus the phenolic hydroxyl group, whose removal obviates the predicted principal route of metabolism and excretion for the compounds, is essential for high inhibitory potency.

A small series of compounds in which the phenolic hydroxyl group had been replaced by amino was prepared (Table 4). The amines were 3−30-fold less potent than the corresponding phenols where direct comparisons could be made (e.g., **4a** vs **2m**, **4b** vs **2o**, **4c** vs **2e**), and the SAR appeared to be similar. Replacement of the MPA phenolic hydroxyl with amino results in a similar decrease in inhibitory potency.[25,26]

In summary, we have found that the MPA hydroxyl group cannot be replaced without major loss in potency. The adjacent substituent must be a hydrogen bond acceptor, with chloro the optimum in size and/or H-bond acceptor ability. These criteria suggest that the inhibitors bind to IMPDH via H-bond donation at the hydroxyl locus and by H-bond acceptance at the adjacent position. In MPA itself, the lactone carbonyl group serves as the H-bond acceptor. A small (>H) lipophilic substituent is required at both the 6- and 7-positions. The role of the 6-substituent may be to influence the conformation of the side chain at C-5.

Representative compounds were tested in vivo, in the mouse Jerne plaque assay.[27] Animals were immunized by intraperitoneal injection of sheep red blood cells (SRBC). Oral administration of immunosuppressant compounds for the 4 subsequent days reduced the in vitro response of the spleen cells to SRBC in a dose-dependent manner. The results are shown in Table 5. The most potent compound was **1l** in which the aromatic methoxyl was replaced by ethyl. This compound is 2−4 times as potent as **1a** in vitro and in vivo. The corresponding methyl-substituted compound **1m** was considerably less potent, despite having in vitro potencies comparable to **1l**. In contrast, the 7-methoxyl analog **1u** showed higher in vivo potency than would be predicted from its in vitro results. Monocyclic compounds, whether phenols (**2d**,**e**), amines (**4c**,**f**), or

Table 5. Inhibition of the Murine PFC Response

		% inhibition, PFC/10^6 WBC @ daily dose (mg/kg)						
compd	potency relative to **1a**	100	75	50	25	12.5	6.25	ED_{50} (mg/kg)
1a	1.0			81 ± 2	36 ± 4	20 ± 4	16 ± 4	33
1l	3.6				93	73	25	9
1m	0.5			45				
1u	0.5			49				
2d	0.3	83, 44		25	0	0		
3b	0.3		36					
4c	0.3	30						
4f	0.3	42						
3l	0.3	32, 40, 28		0				
2e	0	5						
3m	0	0						

compounds in which the phenolic hydroxyl had been replaced by H (**3b**), Cl (**3l**), or F (**3m**), had low in vivo potencies. In general, in vivo potencies correlated with the potencies in the lymphocyte proliferation assay. It is apparent that the possible increase in plasma levels and half-lives which might occur for the non-phenols is not sufficient to overcome the considerable loss of inhibitory potency caused by the replacement of the phenolic group.

Experimental Section

Melting points are uncorrected. Flash chromatography was performed with silica gel A 230−400. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ unless otherwise stated and are reported in ppm downfield of TMS. Microanalyses were within ±0.4% of theory unless otherwise stated.

General Procedure for the Preparation and Claisen Rearrangement of Phenolic Allyl Ethers. The phenol (1 mol), K_2CO_3 (1.5 mol), and allyl bromide (1.5 mol) were stirred in DMF (10 vol) at room temperature for 1−8 h. Water and ether were added, and the organic phase was dried and evaporated. Traces of DMF were removed by percolation through silica gel. Yields of the ethers **11** were ca. 90%. The allyl ether was dissolved in *N*,*N*-diethylaniline (30 mL/g), and the solution was heated in a 200 °C oil bath under N_2 until reaction was complete (TLC, usually about 4 h). The cooled solution was added to 2 N HCl and EtOAc. The organic phase was washed with 2 N HCl and water, dried, and evaporated. The residue was chromatographed on silica gel if necessary. Yields of the rearrangement products **12** were 60−80%.

General Procedure for Conversion of an Allyl Substituent into the MPA Side Chain. 1. Silylation of Phenols. The phenol **12** (1 mol) was dissolved in DMF (10 mL/g), and imidazole (2.0 mol equiv) and *tert*-butylchlorodimethylsilane (1.5 mol equiv) were added. After 8−24 h, water and ether were added. The organic phase was washed with 2 N HCl, dried, and evaporated. The silyl ether was usually used without purification.

2. Ozonolysis of the Allyl Group to the Corresponding Arylacetaldehyde. The allyl compound was dissolved in 1:1 CH_2Cl_2:MeOH (50 mL/g) containing pyridine (0.25%). The solution was cooled to −78 °C, and ozonized O_2 was passed through until a blue color was present. N_2 was then bubbled through to discharge the blue color. Me_2S (3 mol) was added. The reaction mixture was allowed to warm and left overnight. If a starch KI test was negative, the solution was washed with 2 N HCl and aqueous $NaHCO_3$ and then dried and evaporated. The residue was chromatographed to obtain the arylacetaldehyde **13**. Yields were 70−90%.

3. Grignard Reaction To Produce Carbinols 14. The arylacetaldehyde **13** (1.0 mol) was dissolved in THF (20 mL/g), and the solution was cooled to −78 °C. Isopropenyl MgBr (0.7 M in THF, 1.25 mol) was then added. In some cases, an additional 0.25 mol of Grignard reagent was added after 1 h, if appreciable aldehyde was still present. Saturated aqueous NH_4Cl was added, and the cooling bath was removed. Water and ether were added, and the organic phase was dried and evaporated. Chromatography then yielded **14**. Yields were 50−80%.

4. Ortho-Ester Claisen Rearrangement. The carbinol **14** was dissolved in freshly distilled[28] trimethyl orthoformate (20 mL/g). Pivalic acid (0.1 mol equiv) was added, and the solution was heated in a 90 °C bath. When the reaction was complete (TLC, 2−8 h), the cooled solution was added to ether and water. The organic phase was dried and evaporated and the residue chromatographed to give the silyl ether/methyl ester product **15**. Yields were 40−70%.

5. Desilylation.[29] The silyl ether was dissolved in THF (10 mL/g) at 0 °C, and 1.0 M tetrabutylammonium fluoride in THF (1.0 mol equiv) was added. After 10 min the solution was added to water and extracted with EtOAc. The extract was dried and evaporated to give the free phenol. Yields were >90%.

6. Ester Hydrolysis. The methyl ester was dissolved in dimethoxyethane or MeOH (30 mL/g), and a solution of $LiOH·H_2O$ (3 mol equiv) in an equal volume of water was added. When hydrolysis was complete (0.5−2 h), the solution was added to water and washed with ether. The aqueous phase was acidifed with 2 N HCl and extracted with EtOAc. The extract was dried and evaporated, and the residue was recrystallized. Yields were 80−100%.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydrobenzo[*c*]thiophen-5-yl)-4-methyl-4-hexenoic Acid (1b). (a) *tert*-Butyl (*E*)-6-[6-Methoxy-4-[(methoxyethoxy)-methoxy]-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]-4-methyl-4-hexenoate (5a). To a 0 °C solution of methyl mycophenolate (26.2 g, 78.3 mmol) in CH_2Cl_2 (350 mL) were added diisopropylethylamine (19 mL, 109 mmol) and MEM chloride (11.7 g, 94 mmol). After 3 d at room temperature the solution was washed with water and brine, dried ($MgSO_4$), and concentrated to an oil. This material was dissolved in MeOH (400 mL) and treated with 4 N aqueous KOH (80 mL). After 2 d the bulk of the MeOH was removed under reduced pressure and the residue partitioned between EtOAc and cold 0.5 M $NaHSO_4$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give the MEM ether of **1a** (22 g, 69%), mp 90−91 °C (*t*-BuOMe). This material (10.5 g, 25.7 mmol) in EtOAc was treated with oxalyl chloride (4 mL, 46 mmol) and a trace of DMF. After gas evolution was complete (ca. 1 h), the solution was concentrated, redissolved in ethyl acetate (100 mL), and concentrated again. The residue was dissolved in CH_2Cl_2 (30 mL) and added dropwise to a 0 °C solution of *tert*-butyl alcohol (50 mL) and DMAP (4.7 g, 38.5 mmol) in CH_2Cl_2 (75 mL). The solution was allowed to warm to room temperature and stir for 18 h. The reaction mixture was partitioned between EtOAc and cold 1 M aqueous $NaHSO_4$. The organic phase was dried and concentrated and the residue chromatographed on silica gel to give 6.0 g of **5a** as an oil: NMR δ 1.37 (s, 9H), 1.79 (s, 3H), 3.37 (s, 3H), 3.46 (d, J = 6.9 Hz, 2H), 3.57 (m, 2H), 3.76 (s, 3H), 3.94 (m, 2H), 5.12 (s, 2H), 5.22 (br t, J = 6 Hz, 1H), 5.43 (s, 3H).

(b) *tert*-Butyl (*E*)-6-[4-[(Acetylthio)methyl]-2-methoxy-6-[(2-methoxyethoxy)methoxy]-3-methyl-5-(pyrrolidin-1-ylcarbonyl)phenyl]-4-methyl-4-hexenoate (6c). A solution of pyrrolidine (1.4 mL, 16.8 mmol) in THF (30 mL) was treated with 2 M Me_3Al in toluene (8.4 mL, 16.8 mmol). After 30 min, a solution of **5a** (1.96 g, 4.21 mmol) was added and the solution stirred overnight and then heated at 50 °C for 24 h to complete the reaction. After cooling, the reaction mixture was cau-

tiously poured into a slurry of ice and 1 N HCl and then extracted with EtOAc. The organic phase was washed with brine and, aqueous $NaHCO_3$, dried, and stripped to give **6a** as an oil. This material was immediately redissolved in CH_2Cl_2 (35 mL), cooled to −10 °C, and treated sequentially with triethylamine (1.8 mL, 13 mmol) and mesyl chloride (0.8 mL, 10 mmol). After 1 h, ice was added and the mixture partitioned between EtOAc and aqueous 1 M $NaHSO_4$. The organic layer was washed with brine, dried, and concentrated to give **6b**. Thiolacetic acid (0.46 mL, 6.4 mmol) was added to a stirred suspension of Cs_2CO_3 (1.13 g, 3.47 mmol) in DMF (5 mL). After 1 h, a solution of **6b** (ca. 2 g) in DMF (5 mL) was added. After 2 h the reaction mixture was partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was dried, concentrated, and chromatographed (7:3 EtOAc/hexane) to give 1.44 g of **6c** as an oil: NMR δ 1.40 (s, 9H), 1.75 (s, 3H), 1.8−2.0 (m, 4H), 2.2 (s, 3H), 2.23−2.30 (m, 4H), 2.31 (s, 3H), 3.0−3.1 (m, 1H), 3.25−3.4 (m, 3H), 3.37 (s, 3H), 3.54−3.65 (m, 4H), 3.65 (s, 3H), 3.72−3.9 (m, 2H), 4.1 and 4.3 (2d of AB, J = 13.3 Hz, 2H), 5.04 (AB, J = 5.2 Hz, 2H), 5.17 (br t, J = 6 Hz, 1H).

(c) 6c (1.44 g) was dissolved in N_2-flushed MeOH (10 mL). Ammonia was bubbled through the solution for several minutes and the reaction mixture stirred at room temperature until starting material was consumed (ca. 3 h). The reaction was quenched with AcOH and the mixture partitioned between EtOAc and water. The organic layer was dried, concentrated, and then redissolved in EtOAc-AcOH (1:1). After 3 h, the solution was partitioned between EtOAc and water and the organic layer dried and concentrated. Chromatography (7:3 hexane/EtOAc) afforded the MEM ether/*t*-Bu ester of **1b** (0.88 g) as an oil. The MEM group was removed (with concomitant ester exchange) by heating in MeOH (30 mL) containing *p*-TsOH (0.23 g) at reflux for 12 h. Workup and base hydrolysis of the resultant methyl ester gave **1b** (0.16 g): mp 164.5−168 °C (hexane/EtOAc); NMR[30] δ 1.8 (s, 2H), 2.20 (s, 3H), 2.27−2.47 (m, 4H), 3.38 (d, J = 6.8 Hz, 2H), 3.74 (s, 3H), 4.25 (s, 2H), 5.25 (br t, J = 6 Hz, 1H), 9.53 (s, 1H). Anal. ($C_{17}H_{20}O_5S$) C, H.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxoindan-5-yl)-4-methyl-4-hexenoic Acid (1c). 2-(Phenylselenyl)cyclopentenone (**7a**)[31] (15.0 g, 0.063 mol) and 1,3-dimethoxy-1-[(trimethylsilyl)oxy]penta-1,3-diene (**8**)[32] (34.0 g, 0.157 mol) were dissolved in toluene (220 mL). After 24 h at room temperature and 5 h at reflux, the solvent was evaporated and the residue chromatographed (1:4 hexane/EtOAc and then EtOAc) to give **9a** as an oil (5.5g, 46%).[33] This product was dissolved in toluene (180 mL), and DDQ (9.6 g, 1.5 mol equiv) was added in portions over 1 h. The red solution was then evaporated, and the residue was chromatographed (EtOAc/CH_2Cl_2, 1:9) to afford 7-hydroxy-5-methoxy-4-methylindan-1-one (**10a**) (3.55 g, 65%), mp 138−139 °C (EtOAc−hexane). Using procedures described above, **10a** was converted into **1c**: mp 148−149 °C (EtOAc/hexane); NMR[30] δ 1.79 (s, 3H), 2.16 (s, 3H), 2.2−2.36 (m, 2H), 2.36−2.50 (m, 2H), 2.9−3.0 (m, 2H), 3.34 (d, J = 7 Hz, 2H), 3.76 (s, 3H), 5.26 (t, J = 7 Hz, 1H), 9.15 (br, 1H). Anal. ($C_{18}H_{22}O_5$) C, H.

(*E*)-6-(8-Hydroxy-6-methoxy-5-methyl-1-oxoisochroman-7-yl)-4-methyl-4-hexenoic Acid (1d). A solution of the lactone **7b**[34] (7.0 g, 0.033 mol) and 1,3-dimethoxy-1-[(trimethylsilyl)oxy]penta-1,3-diene (**8**)[32] (10.5 g, 0.048 mol) in toluene (150 mL) was refluxed for 18 h. The reaction mixture was brought to dryness, and the crude product was chromatographed (hexane/EtOAc, 3:7) to give **9b** (2.0 g, 18%) as a mixture of isomers. This compound (2.0 g, 6.31 mmol) was dissolved in dichloromethane (250 mL) at 0 °C. *m*-CPBA (1.41 g, 8.17 mmol) was added in portions. After 1 h the solution was added to 20% aqueous $NaHSO_3$; the organic phase was separated, washed with saturated $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue was chromatographed (hexane/EtOAc, 7:3) to obtain 8-hydroxy-6-methoxy-5-methylisochroman-1-one (**10b**) (472 mg, 36%), mp 164−165 °C (EtOAc/hexane). Anal. ($C_{11}H_{12}O_4$) C, H. Using the procedures described above, **10b** was converted into **1d**: mp 160−161 °C (MeOH−ether); NMR[30] (DMSO-d_6) δ 1.73 (s, 3H), 2.15 (s, 3H), 2.23−2.05 (m, 4H), 3.00 (t, J = 7.3 Hz, 2H), 3.26 (d, J = 7.0 Hz, 2H), 3.50 (t, J = 6.7 Hz, 2H), 5.15 (br t, J = 7.0 Hz, 1H). Anal. ($C_{18}H_{22}O_6$·1.25H_2O) C, H.

(*E*)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)-4-methyl-4-hexenoic Acid (1e). 6b (ca. 2 g) was dissolved in DMF (5 mL) and treated with NaN_3 (0.8 g, 12.3 mmol). After 5 h, the mixture was partitioned between hexane−EtOAc (1:1) and water. The organic phase was washed with brine, dried, and concentrated to an oil which was chromatographed (7:3 EtOAc/hexane) to give **6d** (1.38 g) as an oil. This material was dissolved in THF (5 mL) and treated with PPh_3 (0.93 g, 3.5 mmol). After 5 h, water (0.5 mL) and NH_4OH (0.2 mL) were added, and the solution was heated at 50 °C for 4 d to effect hydrolysis of the phosphine imine and lactam formation. The solvents were removed, and the residue was dissolved in MeOH (5 mL) and treated with *p*-TsOH (250 mg). After 1 d the reaction mixture was partitioned between EtOAc and water; the organic layer was washed with aqueous $NaHCO_3$ and brine, dried, and concentrated. Chromatography of the residue (7:3 EtOAc/hexane) gave the *tert*-butyl ester of **1e** (0.73 g) which upon hydrolysis afforded **1e**: mp 179−184 °C (aqueous EtOH); NMR[30] (DMSO-d_6) δ 1.74 (s, 3H), 2.10 (s, 3H), 2.17−2.25 (m, 4H), 3.31 (d, J = 8.1 Hz, 2H), 3.67 (s, 3H), 4.27 (s, 2H), 5.17 (br t, J = 6 Hz, 1H), 8.55 (s, 1H), 8.84 (s, 1H). Anal. ($C_{17}H_{21}NO_5$) C, H, N.

(*E*)-6-(4-Hydroxy-6-methoxy-2,7-dimethyl-3-oxo-2,3-dihydro-1*H*-isoindol-5-yl)-4-methyl-4-hexenoic Acid (1f). To a solution of **1e** (0.042 g, 0.132 mmol) in DMF (1.3 mL) was added NaH (0.052 g of a 60% dispersion in oil, 1.3 mmol). The mixture was stirred at room temperature for 30 min and then recooled to 0 °C and treated with CH_3I (0.022 g, 0.15 mmol). After stirring at 10 °C for 1 h an additional 0.011 g of CH_3I was added and the mixture stirred for an additional 30 min. The reaction was quenched with 1 M aqueous $NaHSO_4$ and the mixture extracted with EtOAc. The organic phase was dried and concentrated to an oil. Chromatography (97:2:1 CH_2Cl_2/MeOH/AcOH) afforded 0.037 g (84%) of **1f**: mp 160−162 °C (EtOAc/hexane); NMR[30] δ 1.80 (s, 3H), 2.13 (s, 3H), 2.28−2.44 (m, 4H), 3.13 (s, 3H), 3.37 (d, J = 6.8 Hz, 2H), 3.71 (s, 3H), 4.22 (s, 3H), 5.28 (br t, J = 6 Hz, 1H). Anal. ($C_{18}H_{23}NO_5$) C, H, N.

(*E*)-6-(4-Hydroxy-6-methoxy-1,7-dimethyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1g). 5b (225 mg, 0.5 mmol) was dissolved in dry DMF (10 mL), and 50% NaH in oil (288 mg, 6.0 mmol) was added. After 15 min MeI (0.3 mL, 4.8 mmol) was added. The reaction mixture was heated to 60 °C for 24 h and then cooled and poured into water. The product was extracted with EtOAc and chromatographed (hexane/EtOAc, 4:1) to give the methyl ester of **1g** (110 mg, 47%) as an oil, NMR[30] δ 0.27 (s, 6H), 1.05 (s, 9H), 1.60 (d, J = 6.8 Hz, 3H), 1.78 (s, 3H), 2.22 (s, 3H), 2.20−2.51 (m, 4H), 3.41 (d, J = 6.2 Hz, 2H), 3.64 (s, 3H), 3.76 (s, 3H), 5.20 (t, J = 6.2 Hz, 1H), 5.40 (q, J = 6.5 Hz, 1H). Basic hydrolysis then gave **1g**: mp 82−84 °C (ether/hexane); NMR[30] δ 1.65 (d, J = 6 Hz, 3H), 1.82 (s, 3H), 2.20 (s, 3H), 2.30−2.50 (m, 4H), 3.39 (d, J = 6.9 Hz, 2H), 3.77 (s, 3H), 5.22 (t, J = 6.5 Hz, 1H), 5.54 (q, J = 6.5 Hz, 1H), 7.84 (s, 1H). Anal. ($C_{18}H_{22}O_6$) C, H.

(*E*)-6-(4,6-Dihydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1h) and (*E*)-6-(6-Ethoxy-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1i). These were prepared as previously described.[19b]

(*E*)-6-(4-Hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1j). The methyl ester of **1h** (500 mg, 1.56 mmol) was dissolved in CH_2Cl_2 (10 mL) at −10 °C, and 2,6-lutidine (1.32 g, 4.68 mmol) and then triflic anhydride (668 mg, 6.2 mmol) were added. After 15 min the mixture was added to water/EtOAc. The organic solution was washed with 2 N $NaHSO_4$ and then dried and evaporated to give **16a** as a gum. This material was stirred in MeOH (15 mL) containing K_2CO_3 (645 mg, 4.68 mmol) for 1 h. The mixture was added to dilute HCl and extracted with EtOAc. The extract was dried and evaporated, and the residue was chromatographed to give **16b** which was converted into the MEM ether **16c** as described above. The latter compound (465 mg, 0.88 mmol) was dissolved in DMF (8 mL) to which Et_3N

(267 mg, 2.6 mmol), formic acid (81 mg, 1.67 mmol), and Pd-(1,1′-bis(diphenylphosphino)ferrocene)Cl_2[35] (37 mg, 0.044 mmol) were added. The reaction mixture was heated at 60 °C for 48 h and then added to water and extracted with EtOAc. The extract was washed with aqueous $NaHSO_4$, dried, and evaporated. The residue was chromatographed (1:1 EtOAc/hexane) to give **17a** (150 mg, 43%), which after removal of the MEM ether and basic hydrolysis gave **1j**: mp 135−139 °C (EtOAc/hexane); NMR[30] (DMSO-d_6) δ 1.70 (s, 3H), 2.16 (s, 3H), 2.15−2.35 (m, 4H), 3.35 (d, J = 6 Hz, 2H), 5.25 (s, 2H), 5.35 (t, J = 7 Hz, 1H), 7.34 (s, 1H). Anal. ($C_{16}H_{18}O_5$) C, H.

(*E*)-6-(4-Hydroxy-7-methyl-3-oxo-6-vinyl-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1k). (a) Methyl (*E*)-4-Methyl-6-[7-methyl-3-oxo-4-[(*p*-tolylsulfonyl)oxy]-6-[[(trifluoromethyl)sulfonyl]oxy]-1,3-dihydroisobenzofuran-5-yl]-4-hexenoate (16d). A mixture of mycophenolic acid (201 g, 0.627 mol), TsOH (3 g, 16 mmol), and MeOH (1.8 L) was stirred at 25 °C for 18 h. The reaction mixture was cooled on ice, and the product **16e** (189.4 g, 90%) was isolated by filtration. A solution of **16e** (70.0 g, 0.209 mol) and TsCl (45.4 g, 0.238 mol) in CH_2Cl_2 (400 mL) was cooled on ice and treated with Et_3N (37.8 mL, 0.27 mol) and DMAP (1.2 g). The reaction mixture was stirred for 1.5 h at 0 °C and then poured into ice water. Extraction with CH_2Cl_2 gave the tosylate **16f** which was used without further purification. The compound was dissolved in collidine (500 mL), LiI (102 g, 0.76 mol) was added, and the reaction mixture was heated at 70 °C with mechanical stirring for 17 h. The mixture was cooled and poured into ice water and concentrated HCl (350 mL). Extraction with EtOAc (6 × 500 mL) gave the phenolic acid **16g**. Esterification as above gave the phenolic ester **16h** (33.7 g). A solution of **16h** (33.7 g, 71 mmol) in CH_2Cl_2 (600 mL) and pyridine (14.6 mL) was cooled to 0 °C and treated with triflic anhydride (13.8 mL, 82 mmol). After 15 min the reaction mixture was poured into 1 N aqueous $NaHSO_4$. Extraction with CH_2Cl_2, drying, and evaporation gave a residue which was recrystallized to give **16d** (39.47 g, 92%): mp 135.7−136.7 °C (EtOAc/hexane). Anal. ($C_{25}H_{25}F_3O_{10}S_2$) C, H.

(b) Methyl (*E*)-4-Methyl-6-[7-methyl-3-oxo-4-[(*p*-tolylsulfonyl)oxy]-6-vinyl-1,3-dihydroisobenzofuran-5-yl]-4-hexenoate (17b). 16d (40.0 g, 65.9 mmol), LiCl (7.74 g, 180 mmol), Ph_3As (2.00 g, 6.5 mmol), tributylvinyltin (21.5 mL, 73.6 mmol), and tris(dibenzylideneacetone)dipalladium(0)−chloroform adduct (0.90 g, 0.98 mmol) were heated in *N*-methylpyrrolidinone (300 mL) at 55 °C for 3 h. The reaction mixture was cooled and poured into a mixture of ice, KF (24 g), water, and EtOAc. After stirring for 1 h at 25 °C this mixture was filtered through Celite and extracted with EtOAc. Concentration of these extracts followed by recrystallization from *t*-BuOMe/EtOAc mixtures gave **17b** (30.52 g, 95%): mp 105.0−106.2 °C. Anal. ($C_{26}H_{28}O_7S$) C, H.

(c) Basic hydrolysis, as described below for **1l**, gave **1k**: mp 148.4−148.7 °C (*t*-BuOMe); NMR[30] δ 1.76 (s, 3H), 2.14 (s, 3H), 2.25−2.5 (m, 4H), 3.41 (d, J = 6.7 Hz, 2H), 5.13 (t, J = 6.7 Hz, 1H), 5.22 (s, 2H), 5.26 (dd, J = 18, 1.7 Hz, 1H), 5.64 (dd, J = 11.6, 1.7 Hz, 1H), 6.66 (dd, J = 18.1, 11.6 Hz, 1H). Anal. ($C_{18}H_{20}O_5$) C, H.

(*E*)-6-(6-Ethyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1l). A solution of the styrene **17b** (29.31 g, 60.5 mmol) in EtOAc (300 mL) and benzene (300 mL) containing tris(triphenylphosphine)rhodium(I) chloride (2.00 g, 2.2 mmol) was hydrogenated at 1 atm for 5 h. The solvent was removed in vacuo and the residue filtered through a short silica gel column (EtOAc). Recrystallization from *t*-BuOMe/EtOAc gave **17c** (28.41 g, 96%), mp 101.3−102.8 °C. Anal. ($C_{26}H_{30}O_7S$) C, H. A mixture of this compound (3.142 g, 6.47 mmol), MeOH (20 mL), water (20 mL), and LiOH (1.2 g, 28.6 mmol) was heated at 62 °C for 17 h. The MeOH was evaporated, and the resulting aqueous solution was poured into 1 N aqueous $NaHSO_4$. Extraction with EtOAc followed by chromatography (EtOAc/hexane with 1% HOAc) gave **1l** (1.417 g, 68%): mp 145.2−145.6 °C (EtOAc/*t*-BuOMe); NMR[30] δ 1.12 (t, J = 7.5 Hz, 3H), 1.81 (s, 3H), 2.16 (s, 3H), 5.21 (s, 2H), 2.30 (m, 2H), 2.45 (m, 2H), 2.68 (q, J = 7.5 Hz, 2H), 3.42 (d, J = 6.3 Hz, 2H), 5.11 (t, J = 6.6 Hz, 1H). Anal. ($C_{18}H_{22}O_5$) C, H.

(*E*)-6-(4-Hydroxy-6,7-dimethyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1m). (a) Methyl 4,5-Dimethyl-2-(prop-2-enyloxy)benzoate (18a). A mixture of 2-hydroxy-4,5-dimethylbenzoic acid[36] (5.00 g, 30 mmol), Li_2CO_3 (5.57 g, 75 mmol), MeI (4.67 mL, 75 mmol), and DMF (50 mL) was stirred at 50 °C for 2 h. After cooling to 25 °C the reaction mixture was poured into ice water, extracted with EtOAc, dried, and evaporated to give methyl 2-hydroxy-4,5-dimethylbenzoate. This ester was added over 30 min to a mixture of NaH (1.48 g, 60%, 37 mmol) and allyl bromide (5.2 mL, 60 mmol) in DMF (30 mL) at 0 °C. After 30 min the reaction mixture was warmed to 25 °C and poured into water. Ether extraction, drying, evaporation, and chromatography (10% EtOAc/hexane) gave **18a** (4.511 g, 68% overall): bp 90 °C/0.10 mmHg. Anal. ($C_{13}H_{16}O_3$) C, H.

(b) *N*,*N*-Diethyl-4,5-dimethyl-2-(prop-2-enyloxy)benzamide (18b). Trimethylaluminum (40 mL, 8.0 mmol, 2 M in toluene) was added to a solution of diethylamine (8.3 mL, 160 mmol) in benzene (80 mL) at 0 °C. The reaction mixture was stirred for 1 h at 25 °C, treated with ester **18a** (8.50 g, 38.6 mmol), and heated at 80 °C for 24 h. The mixture was cooled and poured cautiously into ice water containing HCl (30 mL, concentrated). Isolation by EtOAc extraction and Kugelrohr distillation gave **18b** (9.25 g, 92%): bp 105 °C/0.09 mmHg; mp 57.3−58.2 °C (*t*-BuOMe/hexane). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

(c) *N*,*N*-Diethyl-2-hydroxy-4,5-dimethyl-3-(prop-2-enyl)-benzamide (19a). This was produced by Claisen rearrangement of **18b** as described above: yield 71%; bp 115 °C/0.08 mmHg. Anal. ($C_{16}H_{23}NO_2$) H, N; C: calcd, 73.52; found, 72.79.

(d) 4-[(*tert*-Butyldimethylsilyl)oxy]-6,7-dimethyl-3-oxo-5-(prop-2-enyl)-1,3-dihydroisobenzofuran (20a). Silylation of **19a** gave **19b** (5.66 g, 15.1 mmol) which, in THF (8 mL), was added to a solution of 1.7 M *t*-BuLi in pentane (20 mL, 34 mmol) in THF (40 mL) and TMEDA (4.52 mL) at −90 °C over 30 min. After stirring for 40 min at −90 °C, DMF (9 mL) was added; the reaction mixture was warmed to −15 °C and then poured into ice water. Isolation by EtOAc extraction and chromatography (EtOAc/hexane) gave the aldehyde **19c** (4.35 g, 71%). This compound (4.35 g, 10.8 mmol) was dissolved in EtOH (50 mL) and cooled to 5 °C. Sodium borohydride (225 mg, 6 mmol) was added to the reaction mixture which was stirred at 0 °C for 1 h. The reaction mixture was diluted with ice water, and the carbinol **19d** was isolated by EtOAc extraction and evaporation. This crude product was dissolved in EtOAc (12 mL) and HOAc (3 mL) and heated to 50 °C for 40 min. The reaction mixture was partitioned between EtOAc and aqueous $NaHCO_3$. Extraction with EtOAc followed by recrystallization gave **20a** (2.639 g, 53%): mp 81.1−81.5 °C (*t*-BuOMe/hexane). Anal. ($C_{19}H_{28}O_3Si$) C, H.

(e) Ozonolysis then gave [4-[(*tert*-butyldimethylsilyl)oxy]-6,7-dimethyl-3-oxo-1,3-dihydroisobenzofuran-5-yl]acetaldehyde **(20b)**, 82%, mp 107.8−109.2 °C (*t*-BuOMe/hexane). Anal. ($C_{18}H_{26}O_4Si$) C, H. **20b** was converted into **1m**: mp 167.1−169.7 °C (EtOAc); NMR[30] δ 1.81 (s, 3H), 2.13 (s, 3H), 2.25 (s, 3H), 2.30 (m, 2H), 2.45 (m, 2H), 3.44 (d, J = 6.7 Hz, 2H), 5.09 (t, J = 6.7 Hz, 1H), 5.21 (s, 2H). Anal. ($C_{17}H_{20}O_5$) C, H.

(*E*)-6-(6-Cyclopropyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1n). A mixture of **16d** (1.20 g, 1.98 mmol), Ph_3As (65 mg, 0.21 mmol), LiCl (270 mg, 6.4 mmol), tris(dibenzylideneacetone)-dipalladium(0)−chloroform adduct (40 mg, 0.039 mmol), tributylcyclopropyltin (0.80 mL, 2.45 mmol), and *N*-methylpyrrolidinone (6 mL) was heated at 95 °C for 3 h. An aqueous KF workup and chromatography (as described above for **1k**) gave the ester **17d** (134 mg, 14%). Base hydrolysis then gave **1n**: mp 172.0−173.6 °C (EtOAc/*t*-BuOMe); NMR[30] (DMSO-d_6) δ 0.51 (m, 2H), 1.06 (m, 2H), 1.73 (s, 3H), 2.22 (s, 3H), 2.1−2.3 (m, 4H), 3.58 (d, J = 6.4 Hz, 2H), 5.09 (t, J = 6.4 Hz, 1H), 5.23 (s, 2H). Anal. ($C_{19}H_{22}O_5$) C, H.

(*E*)-6-(4-Hydroxy-7-methyl-3-oxo-6-phenyl-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1o). In a procedure analogous to that described for the preparation of **1n**, the triflate **16d** (0.688 g, 1.13 mmol) on reaction with tributylphenyltin gave the 6-phenyl compound **17e** (0.109 g, 18%). Hydrolysis then gave **1o** (0.050 g, 67%): mp 156.0−

156.5 °C (EtOAc/*t*-BuOMe); NMR[30] δ 1.27 (s, 3H), 1.83 (s, 3H), 2.1−2.4 (m, 4H), 3.12 (d, J = 7.0 Hz, 2H), 5.01 (t, J = 7.0 Hz, 1H), 5.25 (s, 2H), 7.0−7.1 (m, 2H), 7.3−7.5 (m, 3H). Anal. ($C_{22}H_{22}O_5$) C, H.

(*E*)-6-(6-Cyano-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1p). To a solution of **16d** (2.8 g, 4.9 mmol) in dioxane (60 mL) was added KCN (0.644 g, 10 mmol) and $Pd(PPh_3)_4$ (0.80 g, 0.63 mmol). After 5 d at reflux, the mixture was added to water and extracted with EtOAc. The extract was dried and evaporated, and the residue was chromatographed (1:1 EtOAc/hexane) to afford methyl (*E*)-6-(6-cyano-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoate **(17f)** (510 mg, 32%), mp 139−140 °C (EtOAc/hexane); NMR δ 1.84 (s, 3H), 2.4−2.5 (m, 4H), 2.43 (s, 3H), 3.63 (d, J = 7.6 Hz, 2H), 3.64 (s, 3H), 5.23 (s, 2H), 5.23 (t, 1H), 5.28 (s, 2H), 7.90 (s, 1H). Anal. ($C_{18}H_{19}NO_5$) C, H, N. Basic hydrolysis as described above then gave **1p**, mp 142−145.5 °C (EtOAc/hexane); NMR[30] δ 1.84 (s, 3H), 2.3−2.5 (m, 4H), 2.43 (s, 3H), 3.63 (s, 3H), 5.25 (2, J = 7 Hz, 1H), 5.28 (s, 2H), 7.26 (s, 1H). Anal. ($C_{17}H_{17}NO_5$) C, H, N.

(*E*)-6-(6-Carbamoyl-4-hydroxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1q). **17f** (200 mg, 0.6 mmol) was refluxed in 0.7 M aqueous NaOH (7 mL) for 48 h. The solution was then acidified with 2 N HCl and extracted with EtOAc. The extract was dried and evaporated, and the residue was recrystallized from EtOAc/cyclohexane to give **1q** (80 mg, 40%): mp 200.6−202.4 °C; NMR[30] δ 1.69 (s, 3H), 2.09 (s, 3H), 2.12−2.28 (m, 4H), 3.31 (d, J = 10 Hz, 2H), 5.15 (t, J = 6.7 Hz, 1H), 5.28 (s, 2H), 7.67 (d, J = 15 Hz, 1H), 7.86 (d, J = 15 Hz, 1H), 9.4 (s, 1H), 11.99 (s, 1H). Anal. ($C_{17}H_{19}NO_6$) H, N; C: calcd, 61.25; found, 60.59.

(*E*)-6-(4-Hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1r). 4-Hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran[37] was converted into **1r** using the reactions of Scheme 3: mp 145−147 °C (MeOH); NMR[30] (DMSO-d_6) δ 1.71 (s, 3H), 2.13−2.26 (m, 4H), 3.25 (d, J = 6.9 Hz, 2H), 3.85 (s, 3H), 5.11 (t, J = 7 Hz, 1H), 5.23 (s, 2H), 7.64 (s, 1H). Anal. ($C_{16}H_{18}O_6 \cdot 0.25H_2O$) C, H.

(*E*)-6-(7-Ethyl-4-hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1s). (a) 6-Ethyl-3-(2-propenyloxy)-2-cyclohexenone (21b). A solution of *i*-Pr_2NH (16.8 mL, 0.12 mol) in THF (100 mL) was cooled to 0 °C and treated with 1.6 M *n*-BuLi (75 mL, 0.12 mol). The reaction mixture was cooled to −70 °C, and a solution of 3-(2-propenyloxy)-2-cyclohexenone[38] (**21a**) (17.4 g, 0.115 mol) in THF (5 mL) was added over 20 min. EtI (25 mL) and HMPA (15 mL) were added to the reaction mixture. After 17 h at −22 °C, AcOH (10 mL) and water (20 mL) were added and the THF was evaporated. The residue was partitioned between EtOAc and water. Extraction and evaporation gave a residue which was chromatographed to give **21b** (15.2 g, 73%): bp 100 °C/0.11 mmHg. Anal. ($C_{11}H_{16}O_2$) C, H.

(b) Dimethyl 6-Ethyl-3-hydroxy-5-methoxy-4-(2-propenyl)phthalate (24a). A solution of LDA (90 mmol) prepared from *i*-Pr_2NH (12.61 mL, 90 mmol) and 1.6 N *n*-BuLi (56.2 mL, 90 mmol) in THF (120 mL) was cooled to −65 °C and treated with TMSCl (14 mL, 110 mmol). **21b** (15.2 g, 84.4 mmol) in THF (5 mL) was added to the reaction mixture over 15 min. Et_3N (15 mL) was added to the reaction mixture which was poured into hexane/ice water. Separation followed by drying and evaporation gave the silyl enol ether **22** which was diluted with xylene (50 mL), cooled to −50 °C, and treated with dimethylacetylene dicarboxylate (14 mL, 114 mmol) and NaH (100 mg). The reaction mixture was heated at 50 °C for 90 min and at 120 °C for 2 h. The xylene was removed in vacuo, and following an EtOAc/water workup, the crude product was chromatographed on silica gel (EtOAc/hexane) to give phenol **23a** (6.62 g, 36% from **21b**). **23a** (6.62 g, 22.5 mmol) in DMF (40 mL) was treated with K_2CO_3 (6.9 g, 50 mmol) and MeI (4.36 mL, 70 mmol) at 25 °C for 15 h. The reaction mixture was diluted with ice water and extracted with ether. After concentration the residue was recrystallized to give dimethyl 3-ethyl-4-methoxy-6-(2-propenyloxy)phthalate (**23b**) (6.132 g, 88% from **23a**), mp 73.4−74.6 °C (*t*-BuOMe). Anal. ($C_{16}H_{20}O_6$) C, H. Claisen rearrangement then gave **24a** as an oil. Anal. ($C_{16}H_{20}O_6$) C, H.

(c) 7-Ethyl-4-hydroxy-6-methoxy-3-oxo-5-(2-propenyl)-1,3-dihydroisobenzofuran (25a). **24a** (2.80 g, 9.1 mmol), LiOH (2.1 g, 50 mmol), water (25 mL), and MeOH (17 mL) were heated at 53 °C for 4 h. The reaction mixture was cooled on ice and acidified with HCl. Extraction with EtOAc and concentration gave the diacid **24b**. This compound, in HOAc (4 mL), was heated to 90 °C and treated with zinc dust (1.3 g in three portions) over 1.5 h while a solution of HCl (concentrated, 2 mL) in HOAc (2 mL) was added dropwise. The reaction mixture was cooled, diluted with water, and extracted with EtOAc to give **25a** (0.711 g, 31% from **24a**): mp 94.0−95.1 °C (*t*-BuOMe/hexane). Anal. ($C_{14}H_{16}O_4$) C, H.

(d) Silylation followed by side-chain elaboration then gave **1s**: mp 142−145 °C (*t*-BuOMe/hexane); NMR[30] δ 1.20 (t, J = 7.6 Hz, 3H), 1.82 (s, 3H), 2.25−2.5 (m, 4H), 2.59 (q, J = 7.6 Hz, 2H), 3.41 (d, J = 6.7 Hz, 2H), 3.79 (s, 3H), 5.27 (s, 2H), 5.28 (t, J = 6.7 Hz, 1H). Anal. ($C_{18}H_{22}O_6$) C, H.

(*E*)-6-(7-Bromo-4-hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1t).[39] Br_2 (1.81 mL, 3.64 mmol) in CH_2Cl_2 (7 mL) was added to **25b**[40] (200 mg, 0.91 mmol) in CH_2Cl_2 (25 mL). After 1 h the solvent was removed under vacuum, and the residue **26** was dissolved in HOAc (30 mL). Zn dust (250 mg, 325 mesh) was added. After stirring for 36 h the reaction mixture was added to water and extracted with CH_2Cl_2. The extract was washed, dried, and evaporated, and the residue was chromatographed (90:10:1 hexane/EtOAc/HOAc) to give **25c**, 200 mg, 74%; mp 57−58 °C (ether). Anal. ($C_{12}H_{11}BrO_4$) C, H. **25c** was converted into **1t**: mp 154−156 °C (ether) (lit.[39] mp 165−166 °C); NMR[30] (DMSO-d_6) δ 1.71 (s, 3H), 2.16−2.28 (m, 4H), 3.37 (d, J = 7 Hz, 2H), 3.79 (s, 3H), 5.12 (t, J = 7 Hz, 1H), 5.19 (s, 2H). Anal. ($C_{16}H_{17}BrO_6$) C, H.

(*E*)-6-(4-Hydroxy-6,7-dimethoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1u). A solution of 4,6,7-trimethoxy-3-oxo-1,3-dihydroisobenzofuran[41] (1.74 g, 7.76 mmol) in CH_2Cl_2 (150 mL) was added to a suspension of $AlCl_3$ (2.2 g, 16.3 mmol) in CH_2Cl_2 (150 mL). After 26 h at reflux, 10% aqueous HCl (25 mL) was added. After 45 min the organic layer was separated, dried, and evaporated to give 4-hydroxy-6,7-dimethoxy-3-oxo-1,3-dihydroisobenzofuran[42] (1.0 g, 61%). This compound was then converted as described above, except that a modified silylation procedure was required,[43] into **1u**: mp 129−132 °C (ether); NMR[30] δ 1.80 (s, 3H), 2.30−2.46 (m, 4H), 3.37 (d, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 5.23 (t, J = 7 Hz, 1H), 5.32 (s, 2H), 7.26 (s, 1H). Anal. ($C_{17}H_{20}O_7$) C, H.

(*E*)-6-(7-Cyano-4-hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1v) and (*E*)-6-(7-Carbamoyl-4-hydroxy-6-methoxy-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-4-hexenoic Acid (1w). The methyl ester of **1t** (1.2 g, 3.01 mmol) was dissolved in pyridine (20 mL), and Ac_2O (0.71 mL, 7.5 mmol) was added. After 36 h the solution was added to water and extracted with EtOAc. The extract was washed with dilute HCl, dried, and evaporated to give 850 mg (75%) of the phenolic acetate. This material (400 mg, 0.91 mmol) was dissolved in dry dioxane (40 mL), and KCN (106 mg, 1.63 mmol) and $Pd(PPh_3)_4$ (208 mg, 0.2 mmol) were added. After 8 h at 95 °C, additional KCN (100 mg) and $Pd(PPh_3)_4$ (100 mg) were added. After another 12 h at 95 °C, the mixture was added to water. The solution was extracted with EtOAc (discarded) and then acidified with dilute HCl and extracted with EtOAc. The extract was dried and evaporated to give the methyl ester of **1v**[44] (150 mg, 48%). This compound (75 mg, 0.22 mmol) was dissolved in MeOH (5 mL) and water (1 mL), and $LiOH \cdot H_2O$ (19 mg, 0.45 mmol) was added. After 2 h water was added, and the solution was acidified with dilute HCl and then extracted with EtOAc. The extract was dried and evaporated, and the residue was chromatographed (70:30:0.1 hexane/EtOAc/HOAc) to afford **1v**: 35 mg, 45%, mp 125−130 °C (ether/hexane); NMR[30] (DMSO-d_6) δ 1.73 (s, 3H), 2.15−2.25 (m, 4H), 3.29 (d, J = 7 Hz, 2H), 4.03 (s, 3H), 5.07 (t, J = 7 Hz, 1H), 5.41 (s, 2H), 12.0 (br s, 1H). Anal. ($C_{17}H_{17}NO_6$) C, H, N. Also, **1w**: 15 mg, 20%; mp 194−196 °C (ether/hexane); NMR[30] (DMSO-d_6) δ 1.77 (s,

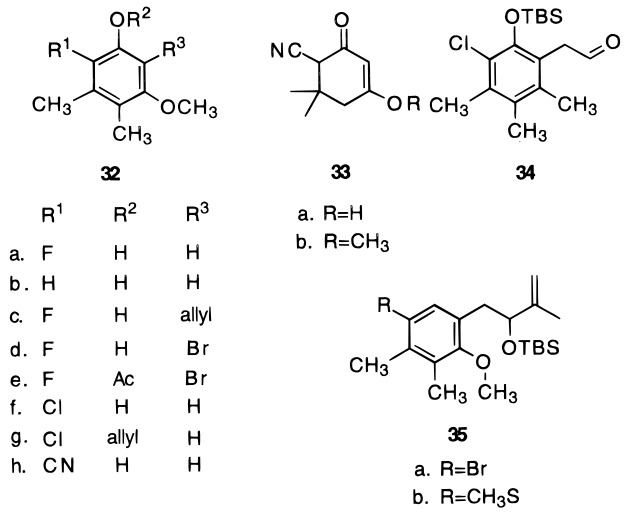
3H), 2.14−2.32 (m, 4H), 3.35 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 5.16 (t, J = 8.4 Hz, 1H), 5.43 (s, 2H), 7.61 (br s, 2H). Anal. ($C_{17}H_{19}NO_7 \cdot 0.25H_2O$) C, H, N.

(*E*)-6-(6-Hydroxy-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (2a). **1a** (5.0 g, 15.6 mmol) and $LiOH \cdot H_2O$ (2.61 g, 62.4 mmol) were refluxed in water (100 mL) for 48 h; then a further 6.0 g (103 mmol) of LiOH was added. After a total of 96 h reflux, the mixture was acidified with dilute HCl and extracted with EtOAc. The extract was dried and evaporated to give the decarboxylated product **27a** (3.55 g, 82%).[45] This material was dissolved in MeOH (50 mL), and *p*-TsOH (90 mg) was added. After 16 h the solution was added to water and extracted with EtOAc. The extract was dried and evaporated and the residue chromatographed (EtOAc/hexane, 1:1) to give the methyl ester **27b** (3.53 g, 95%). The product (3.0 g, 9.7 mmol) was dissolved in acetone (50 mL) at 0 °C, and Cs_2CO_3 (3.16 g, 9.7 mmol) and Ac_2O (0.99 g, 9.7 mmol) were added. After 3 h the mixture was poured into water and extracted with EtOAc. The extract was dried and evaporated and the residue chromatographed (EtOAc/hexane, 1:1) to give the acetate **27c** (2.7 g, 79%). Using the procedures described in the preparation of **1b**, this compound was transformed via the benzylic mesylate to the thioacetate **27d**. This material was added to a refluxing suspension of Raney nickel catalyst (23 g of 50% aqueous suspension) in acetone (250 mL). After 4 h reflux the reaction mixture was filtered through Celite and then evaporated. The residue was partitioned between EtOAc and water. The organic phase was dried and evaporated to give **27e** as an oil. Basic hydrolysis, as described above, then afforded **2a**: mp 92.5−93 °C (hexane/EtOAc); NMR[30] δ 1.82 (s, 3H), 2.09 (s, 3H), 2.16 (s, 3H), 2.28−2.48 (m, 4H), 3.47 (d, J = 7 Hz, 2H), 3.63 (s, 3H), 5.26 (t, J = 7 Hz, 1H), 6.44 (s, 1H). Anal. ($C_{16}H_{22}O_4$) C, H.

(*E*)-6-(2-Hydroxy-6-methoxy-3,4,5-trimethylphenyl)-4-methyl-4-hexenoic Acid (2b). A mixture of **2i** methyl ester (0.36 g, 1.13 mmol) and Zn powder (1.5 g, 23 mmol) in AcOH (10 mL) was heated at 60 °C for 1 h. The solids were filtered off and washed with EtOAc, and the filtrate was washed with water (2×), aqueous $NaHCO_3$, and brine. The organic phase was dried and concentrated, and the residue was chromatographed (85:15 hexane/EtOAc) to give the methyl ester of **2b** (0.3 g), which upon basic hydrolysis afforded **2b**: mp 99−100 °C (hexane); NMR[30] δ 1.79 (s, 3H), 2.12−2.13 (br s, 9H), 2.2−2.33 (m, 4H), 3.32 (d, J = 6.8 Hz, 2H), 3.58 (s, 3H), 5.21 (br t, J = 6 Hz, 1H), 7.9 (br s, 1H). Anal. ($C_{17}H_{24}O_4$) C, H.

(*E*)-6-(3-Fluoro-2-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2c). (a) 2-Fluoro-5-methoxy-3,4-dimethylphenol (32a). Methyl 6-hydroxy-4-methoxy-2,3-dimethylbenzoate[46] (25.0 g) was refluxed in AcOH (75 mL) and concentrated HCl (75 mL) for 40 min. The mixture was added to water and extracted with EtOAc. The extract was dried and evaporated and the residue crystallized from hexane to afford 3-methoxy-4,5-dimethylphenol (**32b**) (14.6 g, 81%), mp 71−73 °C. Anal. ($C_9H_{12}O_3$) C, H. The product (10.0 g, 0.066 mmol) and *N*-fluoropyridinium pyridine heptafluorodiborate (23.4 g, 0.072 mol) were dissolved in acetonitrile (100 mL). After 12 days the solution was added to water and extracted with ether. The extract was washed with 2 N aqueous HCl, dried, and evaporated. The residue was chromatographed (3:1 hexane/ether) to afford **32a** (1.84 g, 15%): mp 57−60 °C (hexane). Anal. ($C_9H_{11}FO_2$) C, H.

(b) 2-Fluoro-5-methoxy-3,4-dimethyl-6-(2-propenyl)-phenol (32c).[47] **32a** (1.8 g, 10.6 mmol) was dissolved in CH_2Cl_2 (50 mL) and MeOH (25 mL) at 0 °C. Tetrabutylammonium tribromide (5.1 g, 10.6 mmol) was added. After 6 h the solution was added to ether/water. The organic solution was dried and evaporated to give 2-bromo-6-fluoro-3-methoxy-4,5-dimethylphenol (**32d**) (2.6 g, 96%), mp 120−123 °C (ether/hexane). Anal. ($C_9H_{10}BrFO_2$) C, H. This material (2.4 g, 0.0096 mol) was dissolved in pyridine (25 mL), and acetic anhydride (4 mL) was added. After 1 h the solution was added to water and extracted with ether. The ethereal solution was washed with 2 N aqueous HCl, dried, and evaporated to afford 2-bromo-6-fluoro-3-methoxy-4,5-dimethylphenyl acetate (**32e**) (2.88 g, 100%), mp 66−68 °C (hexane). Anal. ($C_{11}H_{12}BrFO_3$) C, H. This material (1.97 g, 0.0068 mol) was dissolved in toluene, and allyltributyltin (2.47 g, 0.0075 mol) and $Pd(PPh_3)_4$ (0.371 g, 0.000 32 mol) were added. The mixture was heated at 90 °C for 60 h. Two further additions of 371 mg of Pd catalyst were then made at 24 h intervals. The mixture was then added to water, and the organic solution was dried and evaporated. The residue was chromatographed (100:100:4 hexane/toluene/ether) to afford 2-fluoro-5-methoxy-3,4-dimethyl-6-(2-propenyl)phenyl acetate (794 mg, 43%) as an oil. This material was dissolved in MeOH (10 mL) and water (1.5 mL), to which saturated aqueous Na_2CO_3 (2 mL) was added. The mixture was heated at 50 °C for 4 h and then added to water and extracted with ether. The extract was dried and evaporated to give **32c** (658 mg, 91%) as an oil.



	R^1	R^2	R^3
a.	F	H	H
b.	H	H	H
c.	F	H	allyl
d.	F	H	Br
e.	F	Ac	Br
f.	Cl	H	H
g.	Cl	allyl	H
h.	CN	H	H

Figure 2.

(c) Using the procedures described above, this material was converted in 21% overall yield into **2c**: mp 96−98 °C (ether/hexane); NMR[30] δ 1.81 (s, 3H), 2.13 (s, 3H), 2.14 (d, J = 2 Hz, 3H), 2.3−2.5 (m, 4H), 3.36 (d, J = 7 Hz, 2H), 3.64 (s, 3H), 5.26 (t, J = 7 Hz, 1H). Anal. ($C_{16}H_{21}FO_4$) C, H.

(*E*)-6-(3-Chloro-2-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2d). **32b** (14.6 g, 0.096 mol) and *N*-chlorosuccinimide (12.8 g, 0.096 mol) were dissolved in DMF (100 mL). After 24 h the solution was added to water and extracted with ether. The extract was dried and evaporated, and the residue was chromatographed (4:1 hexane/ether) to afford 2-chloro-5-methoxy-3,4-dimethylphenol (**32f**) (12.8 g, 72%), mp 99−100 °C (hexane/ether). Anal. ($C_9H_{11}ClO_2$) C, H. O-Allylation then gave 2-chloro-5-methoxy-3,4-dimethyl-1-(2-propenyloxy)benzene (**32g**), mp 59−61 °C (MeOH). Anal. ($C_{12}H_{15}ClO_2$) C, H. Claisen rearrangement and side-chain elaboration afforded **2d** in an overall yield of 12%: mp 114−117 °C (aqueous MeOH); NMR[30] δ 1.83 (s, 3H), 2.19 (s, 3H), 2.32 (s, 3H), 2.3−2.5 (m, 4H), 3.41 (d, J = 6 Hz, 2H), 3.67 (s, 3H), 5.30 (t, J = 6 Hz, 1H). Anal. ($C_{16}H_{21}ClO_4$) C, H.

(*E*)-6-(3-Bromo-2-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2e). **27e** (1.99 g, 5.7 mmol) was dissolved in MeOH (30 mL), and K_2CO_3 (3.9 g, 28.5 mmol) was added. After 3 h reflux, the reaction was added to 1 N aqueous $NaHSO_4$ and extracted with EtOAc. The extract was dried and evaporated and the residue chromatographed (4:1 hexane/EtOAc) to give **27f** as an oil. This compound (0.5 g, 1.7 mmol) in CH_2Cl_2 (3 mL) was added to a solution of Br_2 (0.27 g, 1.7 mmol) in a mixture of PhMe (10 mL) and *t*-$BuNH_2$ (0.25 g, 3.4 mmol) at −78 °C. After 3 h the reaction mixture was added to EtOAc/aqueous $NaHSO_4$ containing a few drops of aqueous Na_2SO_3. The organic phase was dried and evaporated, and the residue was subjected to basic hydrolysis to give **2e**: mp 99.5−103.5 °C (hexane/EtOAc); NMR[30] δ 1.80 (s, 3H), 2.19 (s, 3H), 2.34 (s, 3H), 2.2−2.45 (m, 4H), 3.40 (d, J = 6 Hz, 2H), 3.66 (s, 3H), 5.27 (t, J = 7 Hz, 1H). Anal. ($C_{16}H_{21}BrO_4$) C, H.

(*E*)-6-(2-Hydroxy-3-iodo-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2f). A solution of **27f** (0.64 g, 2.2 mmol) in CH_2Cl_2 (1 mL) was added to a solution of *t*-$BuNH_2$

(0.32 g, 4.4 mmol) and I_2 (0.556 g, 2.2 mmol) in PhMe (12 mL) at 0 °C. After 1 h, the reaction mixture was worked up as for **2e** to give the methyl ester of **2f** as an oil (0.9 g, 98%). Basic hydrolysis then afforded **2f**: mp 89−91 °C (*t*-BuOMe/hexane); NMR[30] δ 1.80 (s, 3H), 2.23 (s, 3H), 2.44 (s, 3H), 2.3−2.5 (m, 4H), 3.44 (d, J = 6 Hz, 2H), 3.67 (s, 3H), 5.28 (t, J = 7 Hz, 1H). Anal. ($C_{16}H_{21}IO_4$) C, H.

(*E*)-6-(2-Hydroxy-6-methoxy-4,5-dimethyl-3-nitrophenyl)-4-methyl-4-hexenoic Acid (2g). 27f (0.75 g, 2.6 mmol) was dissolved in pyridine (8.4 mL), and a solution of tetranitromethane (0.60 g, 3.1 mmol) in EtOH (4.8 mL) was added. After 16 h, the mixture was partitioned between EtOAc and aqueous $NaHSO_4$. The organic layer was dried and evaporated and the residue chromatographed (9:1 hexane/EtOAc) to give the methyl ester of **2g** (0.167 g, 19%) as a yellow oil. Basic hydrolysis then gave **2g**: mp 84−86 °C (*t*-BuOMe/hexane); NMR[30] δ 1.79 (s, 3H), 2.18 (s, 3H), 2.41 (s, 3H), 2.25−2.50 (m, 4H), 3.42 (d, J = 6 Hz, 2H), 3.70 (s, 3H), 5.23 (t, J = 7 Hz, 1H). Anal. ($C_{16}H_{21}NO_6$) H, N; C: calcd, 59.43; found, 59.98.

(*E*)-6-(3-Cyano-2-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2h). Ethyl cyanoacetate (56.5 g, 0.5 mol) was added to 1 M ethanolic sodium ethoxide (500 mL, 0.5 mol), and the mixture was stirred for 30 min. Mesityl oxide (49 g, 0.5 mol) was added, and the mixture was heated at reflux for 1 h. The mixture was poured in water and extracted with Et_2O. The aqueous solution was acidified (HCl) and extracted with EtOAc. The extract was washed with 1 N HCl and water, dried, and evaporated, and the residue was crystallized twice from EtOAc/hexane to afford 4-cyano-5,5-dimethyl-1,3-cyclohexanedione **(33a)** (49 g, 60%), mp 129−132 °C. Anal. ($C_9H_{11}NO_2$) C, H, N. This material (10 g, 60.5 mmol) was dissolved in MeOH (100 mL), and trimethyl orthoformate (6.4 g, 60.5 mmol) and *p*-TsOH (57 mg, 0.3 mmol) were added. Two additional portions of trimethyl orthoformate (6.4 g, 60.5 mmol each) were added at 24 h intervals. After 7 d the mixture was added to water and extracted with EtOAc. The extract was washed with H_2O and brine, dried, and evaporated. The residue was chromatographed (CH_2Cl_2/hexane/acetone, 5:5:1) to give 6-cyano-3-methoxy-5,5-dimethylcyclohex-2-enone (**33b**) (3.7 g, 34%), mp 78−80 °C. Anal. ($C_{10}H_{12}NO_2$) C, H, N. The enone (1.9 g, 10.5 mmol) was cooled to 0 °C and cold trifluoroacetic anhydride (20 mL) added. Sulfuric acid (0.64 mL, 11.6 mmol) was added dropwise and the mixture stirred at room temperature for 18 h. The volatiles were evaporated. Ice and solid Na_2CO_3 were added to pH 8. The mixture was reacidified (2 N HCl) and extracted with EtOAc. The extract was dried and evaporated. The residue was chromatographed (EtOAc/hexane, 1:1) to give 2-cyano-5-methoxy-3,4-dimethylphenol[48] (**32h**) (1.2 g, 64%), mp 232−238 °C. Anal. ($C_{10}H_{11}NO_2 \cdot {}^1/_8$EtOAc) C, H, N. Using the procedures described above, the latter was converted into **2h**: mp 112−115 °C (EtOAc/cyclohexane); NMR[30] δ 1.83 (s, 3H), 2.14 (s, 3H), 2.3−2.5 (m, 4H), 2.40 (s, 3H), 3.40 (d, J = 7 Hz, 2H), 3.68 (s, 3H), 5.32 (t, J = 7 Hz, 1H). Anal. ($C_{17}H_{21}NO_4 \cdot {}^1/_4H_2O$) C, H, N.

(*E*)-6-(3-Formyl-2-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2i). A mixture of the methyl ester of **2a** (2.29 g, 7.84 mmol) and hexamethylenetetramine (1.35 g, 9.63 mmol) in AcOH (20 mL) was heated at 60 °C for 24 h.[49] Water (25 mL) was added, and the mixture was stirred at 50 °C for 8 h. The mixture was partitioned between EtOAc and water; the organic phase was washed with brine, dried, and concentrated to an oil. Chromatography (85:15 hexane/EtOAc) afforded the methyl ester of **2i** (1.02 g, 57%) as a low-melting solid. Basic hydrolysis gave **2i**: mp 109−110 °C (hexane/EtOAc); NMR[30] δ 1.80 (s, 3H), 2.15 (s, 3H), 2.26−2.50 (m, 4H), 2.47 (s, 3H), 3.35 (d, J = 7.6 Hz, 2H), 3.7 (s, 3H), 5.26 (br t, J = 6 Hz, 1H), 10.29 (s, 1H), 12.43 (s, 1H). Anal. ($C_{17}H_{22}O_5$) C, H.

(*E*)-6-[2-Hydroxy-3-[(hydroxyimino)methyl]-6-methoxy-4,5-dimethylphenyl]-4-methyl-4-hexenoic Acid (2j). A mixture of the methyl ester of **2i** (0.19 g, 0.59 mmol) and $NH_2OH \cdot HCl$ (0.065 g, 0.94 mmol) in pyridine (1 mL) was stirred at room temperature for 5 h. The mixture was partitioned between EtOAc and aqueous 1 M $NaHSO_4$; the organic layer was dried and concentrated to an oil. Chromatography (4:1 hexane/EtOAc) gave 0.19 g of the methyl ester of **2j**. Basic hydrolysis afforded **2j**: mp 165−166 °C (hexane/EtOAc); NMR[30] (DMSO-d_6) δ 1.80 (s, 3H), 2.15 (s, 3H), 2.15−2.35 (m, 4H), 2.30 (s, 3H), 3.32 (d, J = 6.8 Hz, 2H), 3.67 (s, 3H), 5.23 (br t, J = 6 Hz, 1H), 8.63 (s, 1H), 11.1 (s, 1H), 11.5 (s, 1H). Anal. ($C_{17}H_{23}NO_5$) C, H; N: calcd, 7.21; found, 7.86.

(*E*)-6-[2-Hydroxy-6-methoxy-3-[(methoxyimino)methyl]-4,5-dimethylphenyl]-4-methyl-4-hexenoic Acid (2k). This compound was prepared as above (**2j**) using methoxyamine hydrochloride: mp 112−113 °C (hexane); NMR[30] δ 1.84 (s, 3H), 2.18 (s, 3H), 2.27 (s, 3H), 2.28−2.48 (m, 4H), 3.41 (d, J = 6.6 Hz, 2H), 3.68 (s, 3H), 4.0 (s, 3H), 5.32 (br t, J = 6 Hz, 1H), 8.57 (s, 1H), 10.61 (br s, 1H). Anal. ($C_{18}H_{25}NO_5$) C, H, N.

(*E*)-6-(2-Hydroxy-3,6-dimethoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (2l). This was prepared from 2,5-dimethoxy-3,4-dimethylphenol[50] in an overall yield of 13%: mp 83−86 °C (hexanes); NMR[30] δ 1.80 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 2.35 (m, 2H), 2.44 (m, 2H), 3.36 (d, J = 7 Hz, 2H), 3.64 (s, 3H), 3.78 (s, 3H), 5.31 (t, J = 7 Hz, 1H). Anal. ($C_{17}H_{24}O_5$) C, H.

(*E*)-6-(6-Hydroxy-2,3,4-trimethylphenyl)-4-methyl-4-hexenoic Acid (2m). This was prepared from 3,4,5-trimethylphenol: mp 109.5−111.5 °C (EtOAc/hexane); NMR[30] δ 1.82 (s, 3H), 2.13 (s, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 2.25−2.50 (m, 4H), 3.40 (d, J = 6 Hz, 2H), 5.15 (t, J = 6 Hz, 1H), 6.50 (s, 1H). Anal. ($C_{16}H_{22}O_3$) C, H.

(*E*)-6-(3-Chloro-2-hydroxy-4,5,6-trimethylphenyl)-4-methyl-4-hexenoic Acid (2n). *N*-Chlorosuccinimide (8.5 g, 63.5 mmol) in DMF (400 mL) was added dropwise over 0.5 h to a cooled (0 °C) solution of 3,4,5-trimethylphenol (5.6 g, 31.8 mmol) in DMF (300 mL). The mixture was allowed to warm to room temperature, and after 48 h the reaction was quenched with water and the mixture extracted with ether. The ether layer was stirred with a slurry of zinc and saturated ammonium chloride. The organic layer was dried and evaporated to an orange oil which was chromatographed (50:1 hexanes/EtOAc) to give 1.96 g (29%) of 2-chloro-3,4,5-trimethylphenol as a yellow oil. After O-allylation, Claisen rearrangement, and silylation, ozonolysis gave a mixture so an alternative oxidation was employed. To a solution of 1-[(*tert*-butyldimethylsilyl)oxy]-2-chloro-3,4,5-trimethyl-6-(2-propenyl)benzene (910 mg, 2.8 mmol) in THF/water (1:1) was added OsO_4 (2.5 wt % in 2-methyl-2-propanol, 0.5 mL). After 5 min of stirring, sodium periodate (1.26 g, 5.88 mmol) was added. After 5 h the reaction mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and stripped to a brown oil which was chromatographed (30:1 hexanes/EtOAc) to afford [2-[(*tert*-butyldimethylsilyl)oxy]-3-chloro-4,5,6-trimethylphenyl]acetaldehyde **(34)** (600 mg, 65%), mp 44−45 °C. Anal. ($C_{17}H_{27}ClO_2Si$) C, H, Cl. This compound was then transformed into **2n**: mp 148−150 °C (EtOAc/hexane); NMR[30] δ 1.8 (s, 3H), 2.15 (s, 6H), 2.32 (s, 3H), 2.25−2.4 (m, 4H), 3.4 (d, J = 6.7 Hz, 2H), 5.11 (br t, J = 6.7 Hz, 1H). Anal. ($C_{16}H_{21}ClO_3$) C, H, Cl.

(*E*)-6-(3-Bromo-2-hydroxy-4,5,6-trimethylphenyl)-4-methyl-4-hexenoic Acid (2o). *t*-$BuNH_2$ (0.277 g, 3.8 mmol) was added to PhMe (88 mL) at −25 °C. After 15 min the solution was cooled to −78 °C, and Br_2 (0.276 g, 1.72 mmol) was added. The ethyl ester of **2m** (0.5 g, 1.72 mmol) in CH_2Cl_2 (1 mL) was added. After 1 h the reaction mixture was warmed to room temperature and partitioned between EtOAc and aqueous Na_2SO_3. The organic phase was dried and evaporated and the residue chromatographed to give the ethyl ester of **2o** (0.38 g, 60%). Hydrolysis then afforded **2o**: mp 140−141.5 °C; NMR[30] δ 1.80 (s, 3H), 2.16 (s, 3H), 2.19 (s, 3H), 2.25−2.50 (m, 4H), 2.38 (s, 3H), 3.46 (d, J = 6 Hz, 2H), 5.13 (t, J = 6 Hz, 1H). Anal. ($C_{16}H_{21}BrO_3$) C, H.

(*E*)-6-(2-Hydroxy-4,5,6-trimethyl-3-nitrophenyl)-4-methyl-4-hexenoic Acid (2p). Nitration of the ethyl ester of **2m**, as described above (**2g**), gave 33% of the ethyl ester of **2p** as a yellow oil. Hydrolysis then afforded **2p**: mp 114−117.5 °C (*t*-BuMe ether/hexane); NMR[30] δ 1.80 (s, 3H), 2.19 (s, 3H), 2.22 (s, 3H), 2.25−2.50 (m, 4H), 3.34 (d, J = 6 Hz, 2H), 5.08 (t, J = 6 Hz, 1H). Anal. ($C_{16}H_{21}NO_5$) C, H, N.

(*E*)-6-(5-Chloro-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3a). Using procedures described above, 4-chloro-2,3-dimethylphenol was converted into methyl (*E*)-6-(5-chloro-2-hydroxy-3,4-dimethylphenyl)-4-methyl-4-hexenoate as an oil. This material (200 mg, 0.7 mmol) was dissolved in acetone (25 mL), and K_2CO_3 (2.2 g, 16 mmol) and MeI (0.5 mL, 0.8 mmol) were added. After stirring for 20 h, the mixture was added to water (100 mL) and extracted with EtOAc. The organic layer was washed, dried, and evaporated to afford the methyl ester of **3a** (130 mg, 62%) as a clear oil which was hydrolyzed to give **3a** (oil, 77%): NMR[30] δ 1.73 (s, 3H), 2.22 (s, 3H), 2.32 (s, 3H), 2.3−2.5 (m, 4H), 3.31 (d, J = 7 Hz, 2H), 3.66 (s, 3H), 5.31 (t, J = 7 Hz, 1H), 6.99 (s, 1H). Anal. ($C_{16}H_{21}ClO_3$) C, H.

(*E*)-6-(5-Bromo-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3b). 2,3-Dimethylphenol was converted, as described above, into 2,3-dimethyl-6-(2-propenyl)phenol (67%, oil). Tribromination/reductive debromination, as described above (**1t**), gave 4-bromo-2,3-dimethyl-6-(2-propenyl)-phenol as a yellow oil (5.1 g, 61% overall) which was O-methylated to give 4-bromo-2,3-dimethyl-6-(2-propenyl)anisole (89%), mp 55−56 °C (hexane). This compound was then transformed into **3b**: mp 62−64 °C (EtOH); NMR[30] δ 1.73 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.4−2.5 (m, 4H), 3.31 (d, J = 7 Hz, 2H), 3.74 (s, 3H), 5.31 (t, J = 7 Hz, 1H), 7.18 (s, 1H). Anal. ($C_{16}H_{21}BrO_3 \cdot 0.25H_2O$) C, H.

(*E*)-6-(2-Methoxy-3,4-dimethyl-5-nitrophenyl)-4-methyl-4-hexenoic Acid (3c). To cold TFA (0−5 °C) was added 2,3-dimethyl-6-(2-propenyl)phenol (see preparation of **3b**) (6.7 g, 0.038 mol) followed by dropwise addition of nitric acid (1.7 mL, 0.042 mol). After 15 min, the reaction mixture was poured into H_2O and extracted with EtOAc, and the organic layer was washed, dried, and evaporated to a red oil. Chromatography (19:1 hexane/EtOAc) afforded 2,3-dimethyl-4-nitro-6-(2-propenyl)phenol as a red liquid (2.9 g, 35%). Methylation, as described above, gave 2,3-dimethyl-4-nitro-6-(2-propenyl)anisole which was converted into **3c**: mp 64−65 °C (ether); NMR[30] δ 1.75 (s, 3H), 2.29 (s, 3H), 2.38 (s, 3H), 2.4−2.6 (m, 4H), 3.39 (d, J = 7 Hz, 2H), 3.74 (s, 3H), 5.33 (t, J = 7 Hz, 1H), 7.49 (s, 1H). Anal. ($C_{16}H_{21}NO_5$) C, H, N.

(*E*)-6-(5-Amino-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3d). 3c (150 mg, 0.49 mmol) was dissolved in DMF (3 mL), $NaHCO_3$ (123 mg, 1.46 mmol) and NaS_2O_4 (255 mg, 1.46 mmol) were added, and the mixture was stirred at 60 °C for 4 h. Water was added, and the reaction mixture was acidified with HOAc and extracted with EtOAc and then CH_2Cl_2. Combined organic layers were washed, dried, and evaporated. Chromatography (1:1 EtOAc/hexane 0.1% HOAc) then gave **3d** (35 mg, 26%): mp 130−132 °C (acetone); NMR[30] (DMSO-d_6) δ 1.67 (s, 3H), 1.91 (s, 3H), 2.06 (s, 3H), 2.2−2.3 (m, 4H), 3.14 (d, J = 7 Hz, 2H), 3.48 (s, 3H), 5.20 (t, J = 7 Hz, 1H), 6.27 (s, 1H). Anal. ($C_{16}H_{23}NO_3 \cdot 0.25H_2O$) C, H, N.

(*E*)-6-(5-Hydroxy-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3e). 2,3-Dimethylbenzene-1,4-diol was converted into 4-hydroxy-2,3-dimethylphenyl allyl ether, 35%, mp 96−97 °C (ether), by alkylation with 1 mol of allyl bromide. Silylation and Claisen rearrangement gave 4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethyl-6-(2-propenyl)phenol (61%, oil). The phenol (2.0 g, 6.77 mmol) was dissolved in DMF (60 mL) and cooled to 5 °C. To this were successively added NaOH (325 mg, 8.12 mmol) dissolved in H_2O (3 mL) and dimethyl sulfate (1.4 mL, 14.9 mmol). After 1 h the reaction mixture was partitioned between EtOAc and 10% HCl. The organic layer was dried and evaporated and the residue chromatographed (97:3 hexane/acetone) to give 4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethyl-6-(2-propenyl)anisole (oil, 86%) which was converted into **3e** (36%): mp 127−130 °C (EtOAc); NMR[30] (DMSO-d_6) δ 1.67 (s, 3H), 1.98 (s, 3H), 2.07 (s, 3H), 2.2−2.35 (m, 4H), 3.17 (d, J = 7 Hz, 2H), 3.52 (s, 3H), 5.21 (t, J = 7 Hz, 1H), 8.77 (s, 1H). Anal. ($C_{16}H_{22}O_4$) C, H.

(*E*)-6-(2,5-Dimethoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3f). The methyl ester of **3e** (100 mg, 0.34 mmol) was dissolved in DMF (5 mL), and K_2CO_3 (66 mg, 0.48 mmol) and MeI (26 μL, 0.4 mmol) were added. After 20 h, the reaction mixture was partitioned between H_2O and EtOAc. The organic layer was washed, dried, and evaporated to afford the methyl ester of **3f** (oil, 86%). Basic hydrolysis then gave **3f** (85%): mp 39−40 °C (ether); NMR[30] δ 1.76 (s, 3H), 2.11 (s, 3H), 2.20 (s, 3H), 2.3−2.5 (m, 4H), 3.55 (d, J = 7 Hz, 2H), 3.64 (s, 3H), 3.77 (s, 3H), 5.0 (s, 1H), 5.36 (t, J = 7 Hz, 1H). Anal. ($C_{17}H_{24}O_4 \cdot 0.25H_2O$) C, H.

(*E*)-6-(5-Cyano-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3g). The methyl ester of **3e** was converted via the triflate to the nitrile (see **1p**), which upon basic hydrolysis gave **3g** (60%, foam): MS m/z 287 (M^+), 269, 227, 174; NMR[30] δ 1.73 (s, 3H), 2.22 (s, 3H), 2.43 (s, 3H), 2.4−2.5 (m, 4H), 3.34 (d, J = 7 Hz, 2H), 3.71 (s, 3H), 5.30 (t, J = 7 Hz, 1H).

(*E*)-6-[2-Methoxy-3,4-dimethyl-5-(methylthio)phenyl]-4-methyl-4-hexenoic Acid (3h).[51] **35a** (2.5 g, 6.0 mmol) was dissolved in THF (40 mL), purged with N_2, and cooled to −70 °C. *n*-BuLi (1.6 M in hexane, 5.3 mL, 8.5 mmol) was added dropwise. After 15 min, dimethyl disulfide (0.65 mL, 8.9 mmol) was added dropwise. After 30 min, the reaction was quenched with aqueous NH_4Cl and the mixture partitioned between EtOAc and H_2O. The organic layer was washed, dried, and evaporated. Chromatography (3:1 hexane/toluene) then gave **35b** as an oil (1.6 g, 70%). Desilylation, ortho-ester Claisen rearrangement, and basic hydrolysis then gave **3h** (50%): mp 47−49 °C (hexane); NMR[30] δ 1.75 (s, 3H), 2.22 (s, 3H), 2.29 (s, 3H), 2.35−2.5 (m, 4H), 3.35 (d, J = 7 Hz, 2H), 3.66 (s, 3H), 5.35 (t, J = 7 Hz, 1H). Anal. ($C_{17}H_{24}O_3S$) C, H.

(*E*)-6-[5-(Methylsulfinyl)-2-methoxy-3,4-dimethylphenyl]-4-methyl-4-hexenoic Acid (3i). To the methyl ester of **3h** (200 mg, 0.62 mmol) in CH_2Cl_2 (8 mL) were added wet alumina[52] (620 mg) and Oxone (382 mg, 0.62 mmol), the mixture was heated to reflux for 20 h, cooled, and filtered, and the solvent was removed. Chromatography (3:1 EtOAc/hexane) gave the methyl ester of **3i** (140 mg, 67%) as an oil. Basic hydrolysis then gave **3i** (92%): mp 83−85 °C (hexane); NMR[30] δ 1.73 (s, 3H), 2.22 (s, 3H), 2.25 (s, 3H), 2.4−2.55 (m, 4H), 2.83 (s, 3H), 3.43 (d, J = 7 Hz, 2H), 3.73 (s, 3H), 5.47 (t, J = 7 Hz, 1H), 7.62 (s, 1H). Anal. ($C_{17}H_{24}O_4S$) C, H.

(*E*)-6-(2,3-Difluoro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3j). A solution of 5-amino-2,3-dimethylphenol[53] (10.1 g, 73.6 mmol) in ether (380 mL) and 48% fluoboric acid (74 mL) was chilled with an ice bath while 74 g of 4A molecular sieves was added. After stirring for 1 h at room temperature, it was filtered through glass wool and chilled to 0 °C, and isoamyl nitrite (10.9 mL, 81.1 mmol) was added. After 1 h, the mixture was warmed to room temperature during 0.5 h and then refluxed for 3 h. The reaction mixture was diluted with ether (500 mL) and washed with aqueous $NaHCO_3$ until the washes were alkaline. The ether solution was then dried and evaporated. Chromatography (93:7 hexane/ether) then gave 5-fluoro-2,3-dimethylphenol (3.73 g, 36.2%), mp 71.9−72.8 °C. Anal. (C_8H_9FO) H; C: calcd, 68.56; found, 69.34. This compound (1.52 g, 10.8 mmol) and 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[54] (3.89 g, 11.9 mmol) were refluxed in MeOH (55 mL) for 2.5 h. The reaction mixture was partitioned between EtOAc and brine. The EtOAc solution was dried and evaporated. Chromatography (93:7 hexane/ether) then gave 4,5-difluoro-2,3-dimethylphenol (246 mg, 14%), slightly more polar than the starting material. Using the procedures described above, this compound was converted into **3j**: mp 78.4−78.7 °C (hexane); NMR[30] δ 1.78 (s, 3H), 2.16 (m, 6H), 2.30 (m, 2H), 2.43 (m, 2H), 3.36 (br d, J = 7 Hz, 2H), 3.65 (s, 3H), 5.23 (br t, J = 7 Hz, 1H). Anal. ($C_{16}H_{20}F_2O_3$) C, H.

(*E*)-6-(2-Chloro-3-fluoro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3k). 5-Chloro-2,3-dimethylphenol[46] was fluorinated as described above to give 5-chloro-4-fluoro-2,3-dimethylphenol, 13.3%; mp 84.4−100.6 °C. Anal. (C_8H_8ClFO) C, H. This was converted into **3k**: mp 96.5−97.1 °C (hexane); NMR[30] δ 1.81 (br s, 3H), 2.18 (m, 6H), 2.31 (m, 2H), 2.44 (m, 2H), 3.47 (br d, J = 7 Hz, 2H), 3.64 (s, 3H), 5.18 (br t, J = 7 Hz, 1H). Anal. ($C_{16}H_{20}ClFO_3$) C, H.

(*E*)-6-(2,3-Dichloro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3l). (a) 4,5-Dichloro-2,3-dimethylphenol. 5-Chloro-2,3-dimethylphenol[46] (8.98 g, 57.3 mmol) and *N*-chlorosuccinimide (8.42 g, 63.1 mmol) in DMF

(180 mL) were warmed in a 60 °C oil bath for 3 h. The reaction mixture was partitioned between ether and water. After washing with 250 mL of 10% aqueous Na_2SO_3, the ether layer was dried (Na_2SO_4) and concentrated. Chromatography (95:5 and then 90:10 hexane/acetone) gave the title compound[55] (6.35 g, 58.0%): mp 90−92 °C. Anal. ($C_8H_8Cl_2O$) C, H; Cl: calcd, 37.11; found, 37.79.

(b) Using procedures described above, 4,5-dichloro-2,3-dimethylphenol was converted to **3l**: mp 94−95 °C (hexane); NMR[30] δ 1.81 (br s, 3H), 2.23 (s, 3H), 2.26−2.36 (m, 2H), 2.35 (s, 3H), 2.43 (m, 2H), 3.51 (br d, J = 7 Hz, 2H), 3.65 (s, 3H), 5.18 (br t, J = 6 Hz, 1H). Anal. ($C_{16}H_{20}Cl_2O_3$) C, H.

***(E)*-6-(3-Chloro-2-fluoro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3m).** 5-Fluoro-2,3-dimethylphenol was chlorinated as described above to give 4-chloro-5-fluoro-2,3-dimethylphenol,[55] 71.2%; mp 74−77 °C. Anal. (C_8H_8ClFO) H; C: calcd, 55.03; found, 55.74. This was converted into **3m**: mp 82−83 °C (hexane); NMR[30] δ 1.78 (br s, 3H), 2.19 (s, 3H), 2.28−2.35 (m, 2H), 2.31 (s, 3H), 2.43 (m, 2H), 3.37 (br d, J = 7 Hz, 2H), 3.66 (s, 3H), 5.23 (br t, J = 7 Hz, 1H). Anal. ($C_{16}H_{20}ClFO_3$) C, H.

***(E)*-6-(6-Chloro-2-methoxy-3,4-dimethylphenyl)-4-methyl-4-hexenoic Acid (3n).** This was prepared from 5-chloro-2,3-dimethylphenol:[46] mp 81−83 °C (hexane); NMR[30] δ 1.80 (br s, 3H), 2.15 (s, 3H), 2.20 (s, 3H), 2.30 (m, 2H), 2.43 (m, 2H), 3.45 (br d, J = 7 Hz, 2H), 3.66 (s, 3H), 5.20 (br t, J = 7 Hz, 1H), 6.96 (s, 1H). Anal. ($C_{16}H_{21}ClO_3$) C, H, Cl.

***(E)*-6-(2-Chloro-6-methoxy-4,5-dimethyl-3-nitrophenyl)-4-methyl-4-hexenoic Acid (3o).** A solution of 5-chloro-2,3-dimethyl-6-(2-propenyl)phenol (1.13 g, 5.75 mmol) in AcOH (51.8 mL) and water (5.7 mL) was chilled to 0 °C, and 70% HNO_3 (0.40 mL, 6.3 mmol) was added. After 1.25 h at 0 °C, it was diluted with EtOAc (200 mL) and washed with water, aqueous $NaHCO_3$ until the washes were alkaline, and then brine. After drying the EtOAc solution was evaporated. Chromatography (90:10 hexane/EtOAc) then gave 5-chloro-2,3-dimethyl-4-nitro-6-(2-propenyl)phenol (0.962 g, 69.2%) which was converted into **3o**: mp 101.2−101.9 °C (acetone/hexane); NMR[30] δ 1.80 (br s, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.31 (m, 2H), 2.45 (m, 2H), 3.50 (br d, J = 7 Hz, 2H), 3.69 (s, 3H), 5.15 (br t, J = 7 Hz, 1H). Anal. ($C_{16}H_{20}ClNO_5$) C, H, N.

***(E)*-6-(2-Chloro-3-hydroxy-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3p).** To 2,3-dimethylbenzene-1,4-diol (5.0 g, 36.2 mmol) in DMF (40 mL) was added NCS (5.3 g, 39.8 mmol) in one portion. The reaction mixture was warmed to 60 °C for 3 h and then allowed to cool. The reaction mixture was poured over H_2O (1.5 L) and extracted with EtOAc, and the combined acetate layers were washed, dried, and evaporated. Chromatography (9:1 hexane/EtOAc) then afforded 2.9 g (39%) of 5-chloro-2,3-dimethylbenzene-1,4-diol as an oil. To this material (3.8 g, 22 mmol) in DMF (40 mL) was added DBU (3.9 mL, 26.4 mmol) followed by *t*-$BuMe_2$-SiCl (3.3 g, 22 mmol), and the reaction mixture was allowed to stir at room temperature for 24 h. Reaction was quenched with H_2O (1 L), the mixture was extracted with EtOAc (4 × 100 mL), and the combined acetate layers were washed, dried, and evaporated. Flash chromatography (hexane) afforded 2.0 g (32%) of 4-[(*tert*-butyldimethylsilyl)oxy]-6-chloro-2,3-dimethylphenol as a clear liquid. To a solution of the phenol (2.0 g, 6.97 mmol) in pyridine (20 mL) was added Ac_2O (1.7 mL, 17 mmol) in one portion. After 36 h, the reaction was quenched with H_2O and the mixture extracted with Et_2O (3 × 50 mL). The combined ether layers were washed, dried, and evaporated to afford 4-[(*tert*-butyldimethylsilyl)oxy]-6-chloro-2,3-dimethylphenyl acetate (2.2 g, 96%) as a clear oil. Desilylation (TBAF) then gave 6-chloro-4-hydroxy-2,3-dimethylphenyl acetate which was converted into 2-chloro-4-hydroxy-5,6-dimethyl-3-(2-propenyl)phenyl acetate by allylation/Claisen rearrangement. To a solution of the latter compound (1.4 g, 5.5 mmol) in acetone (40 mL) was added K_2CO_3 (3.0 g, 21.98 mmol) followed by MeI (0.5 mL, 7.7 mmol), and the solution was allowed to stir for 7 h; then the reaction was quenched with H_2O (500 mL), the mixture was extracted with EtOAc (3 × 50 mL), and the combined acetate layers were washed, dried, and evaporated. Chromatography (20:1 hexane/acetone) afforded 2-chloro-4-methoxy-5,6-dimethyl-3-(2-propenyl)phenyl acetate (1.4 g, 95%) as an oil. To this compound (1.2 g, 4.47 mmol) in MeOH (20 mL) and H_2O (8 mL) was added K_2CO_3 (0.92 g, 6.7 mmol). After 20 h the MeOH was removed under vacuum, the residue was diluted with H_2O and extracted with EtOAc, and the combined acetate layers were washed, dried, and evaporated to give 2-chloro-4-methoxy-5,6-dimethyl-3-(2-propenyl)phenol as a light brown oil. Using the previously described procedures, this material was converted into **3p**: mp 60−62 °C (2-propanol); NMR[30] δ 1.80 (s, 3H), 2.18 (s, 6H), 2.28−2.46 (m, 4H), 3.45 (d, J = 6.7 Hz, 2H), 3.62 (s, 3H), 5.17 (t, J = 7.8 Hz, 1H). Anal. ($C_{16}H_{21}ClO_4$) C, H.

***(E)*-6-(2-Chloro-3-cyano-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3q).** Using the procedures described above (**1k**,**p**), the methyl ester of **3p** was converted into the phenolic triflate which was displaced with cyanide using Pd catalysis to give, after ester hydrolysis, **3q**: mp 116−118 °C (ether); NMR[30] δ 1.80 (s, 3H), 2.20 (s, 3H), 2.29−2.45 (m, 4H), 2.47 (s, 3H), 3.48 (d, J = 6.6 Hz, 2H), 3.70 (s, 3H), 5.14 (m, 1H). Anal. ($C_{17}H_{20}ClNO_3$) C, H, N.

***(E)*-6-(3-Bromo-2-chloro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (3r).** 3-Chloro-5,6-dimethyl-2-(2-propenyl)phenol was subjected to bromination/reductive debromination (Zn/AcOH) as described above to give 4-bromo-3-chloro-5,6-dimethyl-2-(2-propenyl)phenol, oil. Anal. ($C_{11}H_{12}BrClO$) C, H. This was converted into **3r**, mp 90−93 °C (hexane); NMR[30] δ 1.80 (br s, 3H), 2.25 (s, 3H), 2.31 (m, 2H), 2.41 (s, 3H), 2.44 (m, 2H), 3.54 (br d, J = 7 Hz, 2H), 3.65 (s, 3H), 5.18 (br t, J = 6 Hz, 1H). Anal. ($C_{16}H_{20}BrClO_3$) C, H.

***(E)*-6-(3-Chloro-6-methoxy-2,4,5-trimethylphenyl)-4-methyl-4-hexenoic Acid (3s).** 4-Chloro-2,3,5-trimethylphenol was converted into 4-chloro-2,3,5-trimethyl-6-(2-propenyl)-phenol, mp 53−54 °C (EtOH). Anal. ($C_{12}H_{15}ClO\cdot 0.125H_2O$) C, H. This was transformed into **3s**: mp 105−107 °C (hexane); NMR[30] δ 1.77 (s, 3H), 2.21 (s, 3H), 2.26 (s, 3H), 2.30 (s, 3H), 2.28−2.42 (m, 4H), 3.39 (d, J = 6.4 Hz, 2H), 3.61 (s, 3H), 5.07 (m, 1H). Anal. ($C_{17}H_{23}ClO_3$) C, H.

***(E)*-6-(6-Amino-2,3,4-trimethylphenyl)-4-methyl-4-hexenoic Acid (4a).** To a solution of 2,3,4,5-tetramethylaniline[56] (2.61 g, 17.5 mmol) in THF (15 mL) was added di-*tert*-butyl dicarbonate (3.9 g, 17.87 mmol). After 24 h the solvent was removed and the residue recrystallized from hexane to give 3.1 g (71%) of *N*-(*tert*-butoxycarbonyl)-2,3,4,5-tetramethylaniline, mp 108−109 °C. To a −78 °C solution of this compound (3.02 g, 12.11 mmol) in THF (40 mL) was added *t*-BuLi[21] (16 mL of a 1.6 M solution in pentane, 25.6 mmol). The yellow solution was allowed to warm to −20 °C and then recooled to −78 °C. Methacrolein (1.8 mL, 21.7 mmol, freshly distilled and dried over Na_2SO_4) was added, the solution was stirred for 5 min, and then the reaction was quenched with aqueous NH_4Cl. The mixture was partitioned between EtOAc and water; the organic phase was washed with brine, dried, and concentrated to give **30** (R = 2,3,4-trimethyl), 1.48 g, 38%; mp 142−143 °C (EtOAc/hexane). Claisen rearrangement of this compound (1.36 g, 4.25 mmol) gave 1.63 g of crude product. This material was dissolved in MeOH (40 mL) and treated with *p*-TsOH·H_2O (1.29 g, 6.78 mmol). The reaction mixture was heated at 50 °C for 12 h and then partitioned between EtOAc and aqueous $NaHCO_3$. The organic phase was dried and concentrated to an oil. Chromatography (4:1 hexane/EtOAc) gave 1.04 g (88%) of the methyl ester of **4a** as an oil. Basic hydrolysis afforded **4a**: mp 176−179 °C (EtOAc); NMR[30] (DMSO-d_6) δ 1.73 (s, 3H), 1.98 (s, 3H), 2.04 (s, 3H), 2.08 (s, 3H), 2.1−2.3 (m, 4H), 3.13 (d, J = 6.4 Hz, 2H), 3.35 (br s, ca. 3 H), 4.93 (br t, J = 6 Hz, 1H), 6.35 (s, 1H). Anal. ($C_{16}H_{23}NO_2$) C, H, N.

***(E)*-6-(2-Amino-3-bromo-4,5,6-trimethylphenyl)-4-methyl-4-hexenoic Acid (4b).** To **4a** methyl ester (0.58 g, 2.1 mmol) in DMF (5 mL) at 0 °C was added a solution of NBS (0.37 g, 2.1 mmol) in DMF (5 mL). The reaction mixture was stirred an additional 15 min; then the reaction was quenched with aqueous Na_2SO_3 and the mixture partitioned between EtOAc and water. The organic phase was dried and concentrated to an oil. Chromatography gave the methyl ester of **4b** (0.29 g), which upon basic hydrolysis afforded **4b** (0.21 g): mp 139−141 °C (hexane/EtOAc); NMR[30] δ 1.75 (s, 3H), 2.07 (s,

3H), 2.1−2.35 (m, 4H), 2.30 (s, 3H), 3.26 (d, J = 6.4 Hz, 2H), 4.53 (br s, 2H), 4.93 (br t, J = 6 Hz, 1H). Anal. ($C_{16}H_{22}BrNO_2$) C, H, N.

(*E*)-6-(2-Amino-3-bromo-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (4c). To 2,3,6-trimethylphenol (22.4 g, 164 mmol) in CH_2Cl_2/MeOH (3:2; 500 mL) at 0 °C was added tetrabutylammonium tribromide (77 g, 162 mmol).[57] After 10 min the reaction was quenched with aqueous $NaHSO_3$. The reaction mixture was partitioned between water and hexane and the organic layer dried and concentrated to give 29.5 g (84%) of 4-bromo-2,3,6 trimethylphenol. A solution of this material (24.1 g, 112 mmol) in CH_2Cl_2 (100 mL) was treated with trifluoroacetic anhydride and DMAP (0.3 g). After 3 h the reaction mixture was concentrated and the residue redissolved in trifluoroacetic acid (50 mL). The solution was cooled to 0 °C and treated dropwise with 90% HNO_3 (10 mL). The reaction mixture was stirred at 0 °C for 1 h, warmed to 20 °C over 1 h, and then poured onto ice. The mixture was extracted with EtOAc and the organic phase washed with water and aqueous $NaHCO_3$, dried, and concentrated. The residue was dissolved in MeOH and treated with excess NH_4OH. After 30 min the reaction mixture was acidified with aqueous HCl and partitioned between EtOAc and H_2O. The combined organic phases were washed, dried, and concentrated. The residue was chromatographed (85:15 hexane/EtOAc) to give 4-bromo-2,3,6-trimethyl-5-nitrophenol (6.2 g, 21%), mp 143−144 °C (hexane/toluene). Methylation (MeI/K_2CO_3/DMF) gave 4-bromo-5-nitro-2,3,6-trimethylanisole, mp 85−86 °C (hexane). This material (6.13 g) was hydrogenated in EtOH containing NaOAc (2 g) over 5% Pd/C (2.5 g). After filtration of the catalyst, the solvent was evaporated and the residue was partitioned between ether and aqueous 1 N NaOH. The organic layer was dried and concentrated to give 3.5 g of 3-methoxy-2,4,5-trimethylaniline, mp 85−86 °C (hexane). Using the methods described above for side-chain elaboration (see **4a**), the aniline was converted into **31** (R = 2-methoxy-3,4-dimethyl, $R^1 = CH_3$). Bromination, as described above for **4b**, gave **4c**: mp 91−94 °C (hexane/EtOAc); NMR[30] δ 1.85 (s, 3H), 2.22 (s, 3H), 2.27−2.51 (m, 4H), 2.37 (s, 3H), 3.45 (d, J = 6.3 Hz, 2H), 3.65 (s, 3H), 5.15 (br t, J = 6 Hz, 1H). Anal. ($C_{16}H_{22}BrNO_3$) C, H; N: calcd, 3.93; found, 3.48.

(*E*)-6-(2-Amino-6-methoxy-4,5-dimethyl-3-nitrophenyl)-4-methyl-4-hexenoic Acid (4d). 31 (R = 2-methoxy-3,4-dimethyl, $R^1 = CH_3$) (0.54 g, 1.85 mmol) and 2,3-dimethyl-2-butene (0.23 g) in pyridine (8 mL) at 0 °C were treated with a solution of tetranitromethane (0.4 g, 2.0 mmol). After 30 min the reaction mixture was partitioned between aqueous 1 M $NaHSO_4$ and EtOAc. The organic phase was washed with brine, dried, and concentrated to an oil. Chromatography (4:1 hexane/EtOAc) afforded the methyl ester of **4d** (0.15 g) which gave **4d** upon base hydrolysis: mp 112−113 °C (hexane/EtOAc); NMR[30] δ 1.86 (s, 3H), 2.17 (s, 3H), 2.25 (s, 3H), 2.35−2.54 (m, 4H), 3.40 (d, J = 6.1 Hz, 2H), 3.67 (s, 3H), 5.12 (br t, J = 6 Hz, 1H), 6.7 (v br s, 1H). Anal. ($C_{16}H_{22}N_2O_5$) C, H; N: calcd, 8.69; found, 8.22.

(*E*)-6-(2-Amino-3-cyano-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (4e). The methyl ester of **4c** (0.165 g, 0.45 mmol), KCN (0.087 g, 1.3 mmol), and $Pd(Ph_3P)_4$ (0.05 g, 0.04 mmol) in dioxane (2 mL) were heated at 100 °C for 18 h. The reaction mixture was partitioned between EtOAc and H_2O and the organic layer dried and concentrated. Chromatography then gave the methyl ester of **4e** (0.06 g, 42%). Basic hydrolysis then gave **4e**: mp 111−112 °C (hexane); NMR[30] δ 1.84 (s, 3H), 2.12 (s, 3H), 2.35−2.53 (m, 4H), 2.38 (s, 3H), 3.33 (d, J = 6.2 Hz, 2H), 3.67 (s, 3H), 5.10 (br t, J = 6 Hz, 1H). Anal. ($C_{17}H_{22}N_2O_3$) C, N; H: calcd, 7.33; found, 8.02.

(*E*)-6-(2-Amino-3-chloro-6-methoxy-4,5-dimethylphenyl)-4-methyl-4-hexenoic Acid (4f). Chlorination of 2,3,6-trimethylphenol (NCS/DMF) gave the 4-chloro product, which after nitration using tetranitromethane, followed by O-methylation, afforded 4-chloro-2,3,6-trimethyl-5-nitroanisole. This compound (3.28 g, 14.28 mmol), Pd/C (5%, 0.3 g), and Et_3N (25 mL) were heated to 90 °C and treated with formic acid portionwise over 48 h until starting material was consumed (ca. 10 mL total of formic acid).[58] The mixture was partitioned between EtOAc and H_2O and the organic phase washed with water, filtered through Celite, and then further washed with aqueous $NaHCO_3$, dried, and concentrated. The residue was suspended in aqueous 1 N HCl and heated at reflux for 24 h. After cooling the reaction mixture was basified with NH_4OH and extracted with hexane/EtOAc (4:1). The organic phase was dried and concentrated. Chromatography (hexane/EtOAc, 9:1) gave 2-chloro-5-methoxy-3,4,6-trimethylaniline (2.3 g). A −78 °C solution of this material (2.08 g, 11.45 mmol) and di-*tert*-butyl dicarbonate (2.9 g, 13.28 mmol) was treated with NaHMDS (25 mL of a 1.0 M solution in THF). After 10 min the reaction mixture was poured into saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was dried, concentrated, and chromatographed (hexane/*t*-BuOMe). The product fractions were concentrated, redissolved in hexane (20 mL), and allowed to crystallize to yield 1.42 g of *N*-(*tert*-butoxycarbonyl)-2-chloro-5-methoxy-3,4,6-trimethylaniline, mp 95 °C (hexane). Side-chain elaboration, N-deprotection, and ester hydrolysis then gave **4f**: mp 92−96 °C (hexane/EtOAc); NMR[30] δ 1.83 (s, 3H), 2.16 (s, 3H), 2.29 (s, 3H), 2.3−2.5 (m, 4H), 3.35 (d, J = 6.4 Hz, 2H), 3.62 (s, 3H), 5.12 (br t, J = 6 Hz, 1H). Anal. ($C_{16}H_{22}ClNO_3$) C, H, N.

Inhibition of IMPDH. The assay for IMPDH activity measures the formation of NADH (λ_{max} = 340 nm, ϵ_{340} = 6220 M^{-1} cm^{-1}) as IMP is converted to XMP by human type II IMP dehydrogenase. Two different buffers and pH conditions were employed. One set of reactions was performed at pH 7.4, in 0.1 M potassium phosphate, 0.5 M KCl, 3 mM EDTA, and 10 μg/mL bovine serum albumin (BSA). The second set of reactions was performed at pH 8.0, in 0.1 M Tris-HCl, 0.1 M KCl, 3 mM EDTA, and 100 μg/mL BSA. The concentrations of the substrates IMP and NAD were 50 and 100 μM (~2 × K_m), respectively. The kinetics of inhibition of the compounds did not differ significantly in the two buffer conditions. Compounds were dissolved and diluted in DMSO or water and assayed for inhibitory activity. DMSO at concentrations above 10% of the total reaction volume significantly inhibited the reaction (~40%); thus, DMSO concentrations were maintained at or below 10% when it was used. The assays contained 0.5−1.0 mL total volume and were initiated by addition of 12.5−25 pmol of recombinant human type II IMPDH (0.0008−0.0016 units).[22] One unit of enzyme catalyzes the formation of 1 μmol of NADH/min at 40 °C at saturating substrate concentrations (200 μM IMP and 400 μM NAD). The reactions were performed in disposable methacrylic plastic microcuvettes (UV transparent, 1 cm path length, 1.5 mL capacity). Enzymatic activity was monitored at 340 nm in a UV/vis spectrophotometer fitted with a water-jacketed multicell transporter maintained at 40 °C by a recirculating bath. The 50% inhibitory value (IC_{50}) for each compound was determined by computer using nonlinear regression fit according to the following equation:

$$\text{fractional activity} = V_0/[(I/IC_{50})^n + 1]$$

where V_0 is the maximum rate, I is the concentration of the compound, and n is the Hill coefficient.

Inhibition of Human Lymphocyte Proliferation.[59] Human peripheral blood mononuclear cells (PBMC) were separated from heparinized whole blood by density-gradient centrifugation in Ficoll-paque (Pharmacia). After washing, 2 × 10^5 cells/well were cultured in microtiter plates with RPMI-1640 (Gibco) supplemented with 5% fetal calf serum, penicillin, and streptomycin. Phytohemagglutinin (PHA; Sigma) was used as a T-cell mitogen at a final concentration of 10 μg/mL. Compounds were tested at four to six different concentrations between 0.001 and 20 μM, by addition to the culture at time 0. Compounds were dissolved in DMSO at 10^{-2} M, and further dilutions were made with RPMI-1640 medium. Cultures were set up in quadruplicate and incubated at 37 °C in an atmosphere of air with 7% CO_2 and 100% humidity for 72 h. A pulse of 0.5 μCi/well [^{3}H]thymidine was added for the last 6 h. Cells were collected on glass fiber filters with an automatic harvester, and radioactivity was measured by standard scintillation procedures. A mean of quadruplicate determinations

was calculated for each compound concentration, and the 50% inhibitory concentration (IC_{50}) for mitogenic stimulation was determined by interpolation, using the cubic spline determination. (Curfit, Interactive Microwave Inc., State College, PA). The results are shown in Tables 1−4.

In Vivo Immunosuppressive Assay. A modification of the Jerne hemolytic plaque (PFC) assay[60] was used. Groups of 5−7 adult C3H or CD-1 female mice (Jackson Laboratories, Bar Harbour, ME, or Charles River, Portage, MI), 10−12 weeks of age, were immunized on day 0 by the ip administration of 1.25×10^8 sheep red blood cells (SRBC) in 0.25 mL of Hanks buffered salt solution (HBSS). Commencing on day 0, each treatment group ($n = 5$) received four consecutive daily doses of the appropriate compound. Test materials were prepared as suspensions in an aqueous vehicle containing 0.9% NaCl, 0.5% sodium carboxymethylcellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol, and 97% distilled water and were delivered in a volume of 0.25 mL. Control animals received aqueous vehicle. On day 4, the mice were euthanized and the spleens were removed and gently dispersed in HBSS; 1 mL of this cell suspension was transferred to a 15 mL tube and diluted to 10 mL with HBSS. The cells were centrifuged for 10 min at 300*g* and resuspended in 10 mL of HBSS. SRBC were washed twice with saline by centrifugation, and the final pellet was resuspended at a final concentration of 20% in HBSS. Guinea pig complement (Gibco), diluted 1:4 in HBSS, was mixed with the SRBC suspension in a 1:1 ratio. A gel consisting of 0.5% agar (Difco) in HBSS was melted in a boiling water bath and then maintained at 47−48 °C. Aliquots (0.7 mL) of the agar solution were dispensed into warmed tubes, and spleen cell suspensions (0.2 mL) and SRBC/complement mixtures (0.1 mL) were added and mixed. Aliquots (0.1 mL) of this mixture were dropped into four separate quadrants of a warmed 47−48 °C Petri dish, and glass coverslips were placed on each. Incubation was carried out for 2−2.5 h at 37 °C in an atmosphere of 5% CO_2 in air. Areas of hemolysis surrounding the plaque-forming cells (PFC) were enumerated with the aid of a dissecting microscope. The data of the four replicates were averaged for each spleen cell suspension, and these averages were used for the calculation of the mean for each experimental group. Total white blood cells/spleen, plaque-forming cells/spleen, and PFC/10^8 WBC were calculated for each spleen. The latter results are shown in Table 5. ED_{50} values for **1a**,**l** were determined graphically; potencies relative to **1a** were estimated for the other compounds.

Acknowledgment. We would like to thank David J. Morgans, Jr. (Institute of Organic Chemistry, Syntex Research), for helpful discussions and suggestions, Ms. Lilia Kurz and Ms. Janis Nelson (Institute of Analytical Research, Syntex Research) for extensive NMR work leading to the assignment of substitution patterns of the polysubstituted benzenes described herein, and Ms. Sandra J. McNabb for assistance in preparing this manuscript.

References

(1) Contribution No. 918 from the Syntex Institute of Organic Chemistry.
(2) Clutterbuck, P. W.; Oxford, A. E.; Raistrick, H.; Smith, G. Studies in the Biochemistry of Micro-organisms. XXIV. The Metabolic Products of the *Penicillium Brevi-compactum* Series. *Biochem. J.* **1932**, *26*, 1441−1458.
(3) (a) Noto, T.; Sawada, M.; Ando, K.; Koyama, K. Some Biological Properties of Mycophenolic Acid. *J. Antibiot.* **1969**, *22*, 165−169. (b) Gallagher, J. A.; Quinn, C. M.; Whittaker, P. A. The action of mycophenolic acid on *Candida albicans*. *Biochem. Soc. Trans.* **1987**, *15*, 290.
(4) Abraham, E. P. The Effect of Mycophenolic Acid on the Growth of *Staphylococcus aureus* in Heart Broth. *Biochem. J.* **1945**, *39*, 398−408.
(5) (a) Williams, R. H.; Lively, D. H.; DeLong, D. C.; Cline, J. C.; Sweeney, M. J.; Poore, G. A.; Larsen, S. H. Mycophenolic acid: Antiviral and Antitumor Properties. *J. Antibiot.* **1968**, *21*, 463−464. (b) Sweeney, M. J.; Cline, J. C.; Williams, R. H. Antitumor and Antiviral Activities of Mycophenolic Acid. *Proc. Am. Assoc. Cancer Res.* **1969**, *10*, 90.
(6) Mitsui, A.; Suzuki, S. Immunosuppressive Effects of Mycophenolic Acid. *J. Antibiot.* **1969**, *22*, 358−363.
(7) Knudtzon, S.; Nissen, N. I. Clinical Trial with Mycophenolic Acid (NSC-129185), a new Antitumor Agent. *Cancer Chemother. Rep.* **1972**, *56*, 221−227.
(8) Epinette, W. W.; Parker, C. M.; Jones, E. L.; Griest, M. C. Mycophenolic acid for psoriasis. *J. Am. Acad. Dermatol.* **1987**, *17*, 962−971.
(9) Carter, S. B.; Franklin, T. J.; Jones, D. F.; Leonard, B. J.; Mills, S. D.; Turner, R. W.; Turner, W. B. Mycophenolic Acid: an Anticancer Compound with Unusual Properties. *Nature* **1969**, *223*, 848−850.
(10) (a) Natsumeda, Y.; Ohno, S.; Kawasaki, H.; Konno, Y.; Weber, G.; Suzuki, K. Two Distinct cDNA's for Human IMP Dehydrogenase. *J. Biol. Chem.* **1990**, *265*, 5292−5295. (b) Konno, Y.; Natsumeda, Y.; Nagai, M.; Yamaji, Y.; Ohno, S.; Suzuki, K.; Weber, G. Expression of Human IMP Dehydrogenase Types I and II in *Escherichia coli* and Distribution in Human Normal Lymphocytes and Leukemic Cell Lines. *J. Biol. Chem.* **1991**, *266*, 506−509.
(11) (a) Natsumeda, Y.; Ikegami, T.; Murayama, K.; Weber, G. De Novo Guanylate Synthesis in the Commitment to Replication in Hepatoma 3924A Cells. *Cancer Res.* **1988**, *48*, 507−511. (b) Nagai, M.; Natsumeda, Y.; Konno, Y.; Hoffman, R.; Irino, S.; Weber, G. Selective Up-Regulation of Type II Inosine 5′-Monophosphate Dehydrogenase Messenger RNA Expression in Human Leukemias. *Cancer Res.* **1991**, *51*, 3886−3890.
(12) Allison, A. C.; Eugui, E. M. Immunosuppressive and other Effects of Mycophenolic Acid and an Ester Prodrug, Mycophenolate Mofetil. *Immunol. Rev.* **1993**, *136*, 5−28.
(13) Lee, W. A.; Gu, L.; Miksztal, A. R.; Chu, N.; Leung, K.; Nelson, P. H. Bioavailability Improvement of Mycophenolic Acid Through Amino Ester Derivatization. *Pharm. Res.* **1990**, *7*, 161−166.
(14) Goldblum, R. Therapy of rheumatoid arthritis with mycophenolate mofetil. *Clin. Exp. Rheumatol.* **1993**, *11* (Suppl. 8), S117−S119.
(15) (a) Deierhoi, M. H.; Kauffman, R. S.; Hudson, S. L.; Barber, W. H.; Curtis, J. J.; Julian, B. A.; Gaston, R. S.; Laskow, D. A.; Diethelm, A. G. Experience with Mycophenolate Mofetil (RS61443) in Renal Transplantation at a Single Center. *Ann. Surg.* **1993**, *217*, 476−484. (b) Ensley, R. D.; Bristow, M. R.; Olsen, S. L.; Taylor, D. O.; Hammond, E. H.; O'Connell, J. B.; Dunn, D.; Osburn, L.; Jones, K. W.; Kaufmann, R. S.; et al. The use of mycophenolate mofetil (RS-61443) in human heart transplant recipients. *Transplantation* **1993**, *56*, 75−82. (c) Taylor, D. O.; Ensley, R. D.; Olsen, S. L.; Dunn, D.; Renlund, D. G. Mycophenolate Mofetil (RS-61443): Preclinical, Clinical and Three-year Experience in Heart Transplantation. *J. Heart Lung Transplant.* **1994**, *13*, 571−582.
(16) Nelson, P. H.; Eugui, E.; Wang, C. C.; Allison, A. C. Synthesis and Immunosuppressive Activity of Some Side-Chain Variants of Mycophenolic Acid. *J. Med. Chem.* **1990**, *33*, 833−838.
(17) Ohsugi, Y.; Suzuki, S.; Takagaki, Y. Antitumor and Immunosuppressive Effects of Mycophenolic Acid Derivatives. *Cancer Res.* **1976**, *36*, 2923−2927.
(18) (a) Sweeney, M. J.; Hoffman, D. H.; Poore, G. A. Possible in Situ Activation of Mycophenolic Acid by β-Glucuronidase. *Cancer Res.* **1971**, *31*, 477−478. (b) Sweeney, M. J.; Hoffman, D. H.; Esterman, M. E. Metabolism and Biochemistry of Mycophenolic Acid. *Cancer Res.* **1972**, *32*, 1803−1809. (c) Matsuzawa, Y.; Nakase, T. Metabolic fate of ethyl O-[N-(p-carboxyphenyl)-carbamoyl]mycophenolate (CAM), a new antitumor agent, in experimental animals. *J. Pharmacobio-Dyn.* **1984**, *7*, 776−783.
(19) (a) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. A Total Synthesis of Mycophenolic Acid, Some Analogues and Some Biogenetic Intermediates. *Tetrahedron* **1972**, *28*, 4395−4404. (b) Jones, D. F.; Mills, S. D. Preparation and Antitumor Properties of Analogs and Derivatives of Mycophenolic Acid. *J. Med. Chem.* **1971**, *14*, 305−311. (c) Lee, J.; Anderson, W. K. A Facile Synthesis of an (E)-4-Methyl-4-hexenoic Acid Substituted Pyridine Analogue of Mycophenolic Acid. *Synth. Commun.* **1992**, *22*, 369−376. (d) Beisler, J. A.; Hillery, S. S. Antitumor Agents II: Nitrogen Analogs of Mycophenolic Acid. *J. Pharm. Sci.* **1975**, *64*, 84−87. (e) Jones, D. F.; Moore, R. H.; Crawley, G. C. Microbial Modification of Mycophenolic Acid. *J. Chem. Soc. C* **1970**, 1725−1737. (f) Lai, G.; Anderson, W. K. A Concise Synthesis of a Benzimidazole Analogue of Mycophenolic Acid using a BF_3-Et_2O Catalysed Amino-Claisen Rearrangement. *Tetrahedron Let.* **1993**, *34*, 6849−6852. (g) Anderson, W. K.; Boehm, T. L.; Makara, G. M.; Swann, R. T. Synthesis and Modeling Studies with Monocyclic Analogues of Mycophenolic Acid. *J. Med. Chem.* **1996**, *39*, 46−55.
(20) Patterson, J. W.; Huang, G. T. The Orthoester Claisen Rearrangement in the Synthesis of Mycophenolic Acid. *J. Chem. Soc., Chem. Commun.* **1991**, 1579−1580.
(21) Clark, R. D.; Muchowski, J. M.; Souchet, M.; Repke, D. B. Synthesis of Protected Indoles from N-tert-Butoxycarbonyl-2-alkylanilines. *Synlett* **1990**, 207−208.

(22) Carr, S. F.; Papp, E.; Wu, J. C.; Natsumeda, Y. Characterization of Human Type I and Type II IMP Dehydrogenases. *J. Biol. Chem.* **1993**, *268*, 27286−27290.
(23) Sweeney, M. J.; Gerzon, K.; Harris, P. N.; Holmes, R. E.; Poore, G. A.; Williams, R. H. Experimental Antitumor Activity and Preclinical Toxicology of Mycophenolic Acid. *Cancer Res.* **1972**, *32*, 1795−1802.
(24) Molar refractivity values were used to compare the size of substituents. Kubinyi, H. *QSAR: Hansch Analysis and Related Approaches*; VCH: New York, 1993; pp 21−27.
(25) Sjogren, E. B. Unpublished results from these laboratories, 1990. See also: Sjogren, E. B. 4-Amino Derivatives of Mycophenolic Acid. U.S. Patent 5,441,953, 1995.
(26) Or, Y. S.; Liu, L.; Lane, B.; Hsieh, G.; Sweeney, D.; Mollison, K. W.; Luly, J. R. Design and synthesis of mycophenolic acid analogs as potential immunosuppressants. Division of Medicinal Chemistry, 208th National Meeting of the American Chemical Society, Washington, DC, August 1994; Poster 112.
(27) Jerne, N. K.; Henry, C.; Nordin, A. A.; Fuji, H.; Koros, A. M. C.; Lefkovits, I. Plaque forming cells: Methodology and theory. *Transplant. Rev.* **1974**, *18*, 130−191.
(28) Appreciably higher yields were obtained if the ortho-ester was distilled immediately prior to use.
(29) Both the silyl ether and methyl ester groups could be removed in one step, using LiOH in 1:1 aqueous glyme at 60 °C for 2−4 h.
(30) Side-chain resonances for all final compounds are approximately as follows: δ 1.7−1.8 (s, CH_3), 2.2−2.5 (m, $(CH_2)_2$), 3.25−3.40 (d, $J = \sim 7$ Hz, $ArCH_2$), 5.15−5.35 (t, $J = \sim 7$ Hz, =CH).
(31) Liotta, D.; Saindane, M.; Barnum, C.; Zima, G. Synthetic Applications of 2-Phenylselenylenones-III. An Overview. *Tetrahedron* **1985**, *41*, 4881−4889.
(32) Watanabe, M.; Tsukazaki, M.; Hamada, Y.; Iwao, M.; Furukawa, S. An Efficient Synthesis of Phthalides by Diels-Alder Reaction of Sulphur-Substituted Furanones with Silyloxydienes: a Formal Synthesis of Mycophenolic Acid. *Chem. Pharm. Bull.* **1989**, *37*, 2948−2951.
(33) The product was obtained as a 3.5:1.5:1 mixture of isomers. The loss of the phenylselenyl group was unexpected.
(34) Kato, M.; Ouchi, A.; Yoshikoshi, A. A Useful Synthetic Method for 3-Substituted δ-Lactones. Synthesis of (±)-Secocrispiolide. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1479−1486.
(35) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. Palladium-Catalysed Carbonylation of Aryl Triflates. Synthesis of Arenecarboxylic Acid Derivatives from Phenols. *Tetrahedron Lett.* **1986**, *27*, 3931−3934.
(36) Schmitt, G.; An, N. D.; Poupelin, J.-P.; Vebrel, J.; Laude, B. A New and Mild Synthesis of Substituted Salicylic Acids. *Synthesis* **1984**, 758−760.
(37) Birch, A. J.; Wright, J. J. A Total Synthesis of Mycophenolic Acid. *Aust. J. Chem.* **1969**, *22*, 2635−2644.
(38) Patterson, J. W. The Synthesis of Mycophenolic Acid. *Tetrahedron* **1993**, *49*, 4789−4798.
(39) A synthesis of this compound in which *Penicillium brevicompactum* was used to attach the side chain to the nucleus has been reported; see: Canonica, L.; Rindone, B.; Scolastico, C.; Aragozzini, F.; Craveri, R. Halogenated Analogues of Mycophenolic Acid. *J. Chem. Soc., Chem. Commun.* **1973**, 222−223.
(40) Intermediate in the preparation of **1r**, structure presented in Scheme 6.
(41) Evans, G. E.; Staunton, J. An Investigation of the Biosynthesis of Citromycetin in *Penicillium frequentans* using ^{13}C and ^{14}C-Labelled Precursors. *J. Chem. Soc., Perkin Trans. 1* **1988**, 755−761.
(42) As expected, cleavage occurred selectively at the methoxyl group ortho to the carbonyl. Structure assigned from a two-dimensional long-range $^1H-^{13}C$ heteronuclear NMR correlation experiment.
(43) Silylation was effected quantitatively by reaction with 1.5 equiv of *tert*-butyldimethylsilyl triflate and 1.5 equiv of 2,6-lutidine in CH_2Cl_2 for 30 min.
(44) The phenolic acetate was removed during the cyanation reaction, and the resultant *p*-cyanophenol was soluble in aqueous KCN.
(45) A lower-yielding preparation of this compound is described in ref 19b.
(46) Nelson, P. H.; Nelson, J. T. Synthesis of Tetra- and Pentasubstituted Benzenes from Dimedone and Derivatives. *Synthesis* **1992**, 1287−1291.
(47) Attempted preparation of this compound by Claisen rearrangement of the appropriate allyl ether yielded a complex mixture. The following four-step procedure was therefore used.
(48) Made by analogy to a published process for aromatization of dimedone derivatives, ref 46.
(49) Mori, K.; Sato, K. A General Synthetic Method for Prenylated Phenols of Microbial Origin. Synthesis of Colletochlorins A and B. *Tetrahedron* **1982**, *38*, 1221−1225.
(50) Burnell, R. H.; Ringuet, M. Synthesis of dehydrocycloroyleanone. *Can. J. Chem.* **1978**, *56*, 517−521.
(51) The methylthio group was introduced by lithiation, followed by reaction with dimethyl disulfide, of the silyl-protected allylic carbinol intermediate in the preparation of **3b**.
(52) Greenhalgh, R. P. Selective Oxidation of Phenyl Sulphides or Sulphoxides or Sulphones Using Oxone® and Wet Alumina. *Synlett* **1992**, 235−236.
(53) (a) Crossley, A. W. Derivatives of o-Xylene. Part VI. 5-Bromo-o-3-xylenol. *J. Chem. Soc.* **1913**, 2179−2182. (b) Alexsandrov, I. V.; Abradushkin, Y. S. Derivatives of 3-Aminophenol I. N-Arylsulfonyl and N-Benzoyl Derivatives of 3-Aminophenol and Its Homologs. *J. Gen. Chem. USSR (Engl. Transl.)* **1960**, *30*, 3374−3379.
(54) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Salts: a Novel Family of Electrophilic Fluorinating Agents. *J. Chem. Soc., Chem. Commun.* **1992**, 595−596.
(55) The structure of the product was determined by one- and two-dimensional NMR spectroscopy. One- and three-bond shift-correlation spectroscopy was used to establish H−C and H−C−C connectivity, and NOE difference methods were used to identify adjacent substituents on the aromatic ring.
(56) Prepared by dehydrogenation of 2,3,4,5-tetramethylnitrobenzene; see: Olah, G. A.; Lin, H. C. Synthetic Methods and Reactions; VI. Boron Trifluoride Catalyzed Mononitration of Tetramethylbenzenes and Pentamethylbenzene with Methyl Nitrate in Nitromethane Solution. A New Selective Nitration Method. *Synthesis* **1973**, 488−490.
(57) Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. Bromination of Phenols by Use of Benzyltrimethylammonium Tribromide. *Chem. Lett.* **1987**, 627−630.
(58) Cortese, N. A.; Heck, R. F. Palladium-Catalyzed Reductions of Halo- and Nitroaromatic Compounds with Triethylammonium Formate. *J. Org. Chem.* **1977**, *42*, 3491−3494.
(59) Eugui, E. M.; Almquist, S. J.; Muller, C. D.; Allison, A. C. Lymphocyte-Selective Cytostatic and Immunosuppressive Effects of Mycophenolic Acid in Vitro: Role of Deoxyguanosine Nucleotide Depletion. *Scand. J. Immunol.* **1991**, *33*, 161−173.
(60) (a) Jerne, N. K.; Nordin, A. A.; Henry, C. The Agar Plaque Technique for Recognizing Antibody-producing Cells. In *Cell-bound Antibodies*; Amos, B., Koprowski, H., Eds.; Wistar Institute Press: Philadelphia, 1963; pp 109−125. (b) Mishell, R. I.; Dutton, R. W. Immunization of Normal Mouse Spleen Cell Suspensions in Vitro. *Science* **1966**, *153*, 1004−1006.

JM9603633