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3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 2. Structural Modification of 7-(Substituted aryl)-3,5-dihydroxy-6-heptenoic Acids and Their Lactone Derivatives

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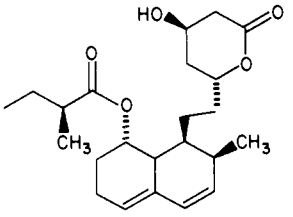
A series of 7-(substituted aryl)-3,5-dihydroxy-6-heptenoic (heptanoic) acids and their lactone derivatives have been prepared and tested for inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase in vitro. A systematic exploration of the structure–activity relationships in this series led to the synthesis of (+)-*trans*-(*E*)-6-[2-[2,4-dichloro-6-[(4-fluorophenyl)methoxy]phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (**66**(+)), which has one-half of the inhibitory activity of compactin.

Subsequent to the first reports disclosing the structure[1] and biological activity[2] of compactin (ML-236B, 1), a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a series of studies directed toward the development of structurally simplified HMG-CoA reductase inhibitors were initiated in these laboratories. Our initial investigation[3] afforded a series of modestly active 5-substituted 3,5-dihydroxypentanoic acids and their derivatives whose intrinsic inhibitory potencies were determined by (a) the stereochemistry of the lactone moiety, (b) the ability of the lactone moiety to be opened to a dihydroxy acid, (c) the length of the moiety bridging the lactone and the lipophilic groups, and (d) the size and shape of the lipophilic group. In this report we describe further modifications of the lipophilic group which led to a series of 7-(substituted phenyl)-3,5-dihydroxy-6-heptenoic (heptanoic) acids and their lactone derivatives with improved intrinsic inhibitory potencies (i.e., up to 50% that of 1).



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Chemistry. The 6-substituted 4-hydroxypyran-2-ones explored in this study were prepared by the general method outlined in Scheme I and are listed in Tables I and II. The requisite alkyloxy- and benzyloxy-substituted benzaldehydes (e.g., **3**) were prepared by the alkylation of the appropriate phenolic precursor (e.g., **2**) with an alkyl or benzyl halide in DMF containing K_2CO_3 and are listed in Table III. The general methods of Baker[4] (A), Wittig[5] (B), and Wollenberg[6] (C) were used to prepare the intermediate propenals (e.g., **4**) which are described in Tables IV and V. Condensation of propenal **4** with the dianion of methyl acetoacetate followed by sodium borohydride reduction, basic hydrolysis, acidification, and lactonization (by azeotropic removal of H_2O) gave a mixture of trans **7a(±)** and cis **7b(±)** lactones which were separated by column chromatography. The ethylene bridge of the trans lactone **7a(±)** as reduced catalytically to provide the ethyl-bridged compound **8a(±)**. Lactone **8a(±)** was resolved by formation of the diastereomeric α-methylbenzylamides which were separated by chromatography. After amide hydrolysis, each acid was relactonized to provide the respective lactones **8a(+)** and **8a(−)**.

Preparation of aldehyde **16** required for the elaboration of lactone **39** is shown in Scheme II. Tetralone **9** was converted to silyl enol ether **10** which was ozonized and reduced to provide acid **11**. After protection of the carboxylic acid group in **11** as its methyl ester (**12**), treatment with $SOCl_2$ gave chloride **13** which, in turn, was converted to ether **14** with sodium 4-fluorophenoxide. Reduction of the ester **14** with LAH followed by oxidation of the resulting alcohol **15** with pyridinium chlorochromate gave aldehyde **16**.

(Methylthio)methyl (MTM) ether **17** and (methoxyethoxy)methyl (MEM) ether **18** were prepared as intermediates for the synthesis of phenol **19** which, in principle, could be used as starting material in a one-step synthesis

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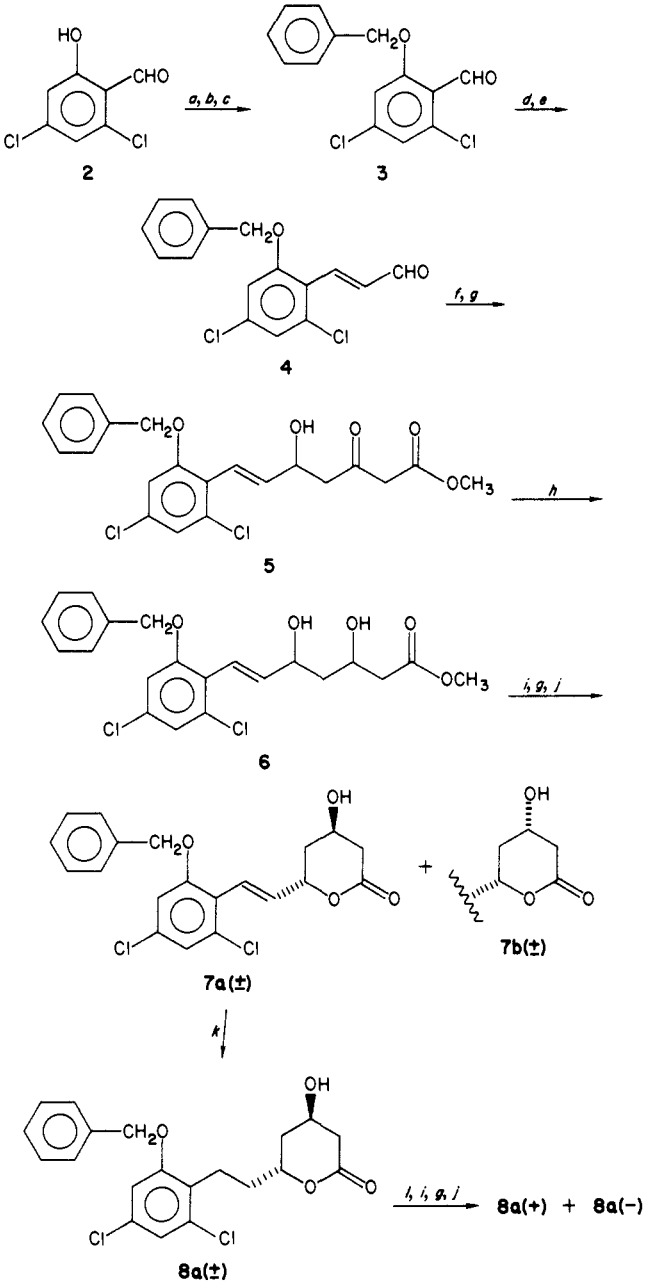
(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hansenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(2) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346.
(3) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
(4) Baker, B. R.; Janson, E. E.; Vermeulen, N. M. J. *J. Med. Chem.* **1969**, *12*, 898.
(5) Wittig, G.; Hesse, A. "Organic Synthesis"; Breslow, R., Ed.; Wiley: New York, 1970; Vol. 50, p 66.
(6) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365.

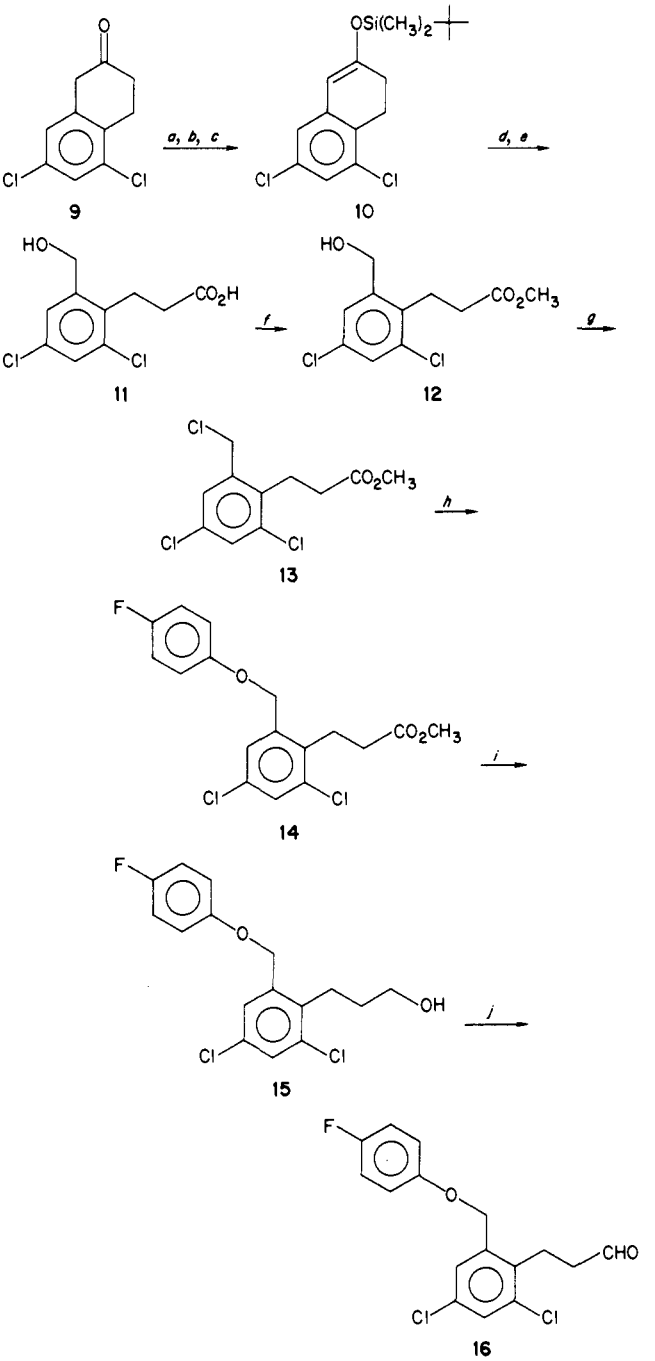
0022-2623/86/1829-0159$01.50/0

Scheme I



[a] K_2CO_3. [b] $C_6H_5CH_2Br$. [c] DMF. [d] $LiCH{=}CHOC_2H_5$. [e] Silica gel. [f] $CH_2COCH_2CO_2CH_3$. [g] H^+. [h] $NaBH_4$, EtOH. [i] OH^-. [j] $C_6H_5CH_3$, Δ. [k] H_2, Rh/C. [l] R-(−)-$C_6H_5CH(CH_3)NH_2$.

Scheme II



[a] LDA, −78 °C. [b] HMPA. [c] t-BuSiMe$_2$Cl. [d] O_3, MeOH, −78 °C. [e] $NaBH_4$. [f] CH_3I, DMF, $NaHCO_3$. [g] $SOCl_2$. [h] 4-$FC_6H_4O^-Na^+$, DMF. [i] LAH, Et_2O. [j] Pyridinium chlorochromate, CH_2Cl_2.

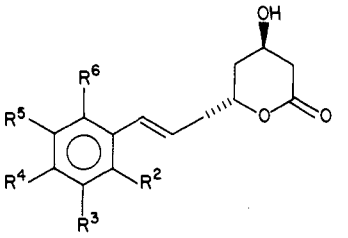
of a large variety of 6-substituted ether derivatives. As indicated in Scheme III, several attempts to cleave MEM ether **18** were unsuccessful, whereas cleavage of MTM ether **17** by the procedure of Holton[10] gave the butyric acid derivative **20**. A similar ring closure was observed previously when propenal **101** was treated under identical conditions.[11] If the ethylene bridge of **18** was first reduced (**21**), the MEM ether could be cleaved using Corey's[12] conditions to give phenol **22** contaminated with MEM ether **23** (formed by intramolecular migration of the MEM moiety). However, this procedure afforded **22** in low yields and was not a practical method for preparing the target 6-substituted ethers.

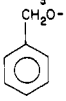
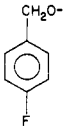
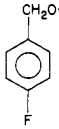
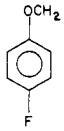
Biological Results and Discussion

The ring-opened sodium dihydroxycarboxylate forms of the compounds listed in Tables I and II were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase. The results of substitution on the phenyl ring are shown in Table I. Monosubstitution of the phenyl ring greatly increased the inhibitory potency. A fivefold increase in inhibitory potency was realized when a phenyl group was placed in the para position (**25**). Movement of the phenyl group to the ortho position (**26**)

(7) Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285. Leusink, A. J.; Budding, H. A.; Drenth, W. *Ibid.* **1968**, *11*, 541.
(8) Weiler, L.; Huckin, S. N. *Tetrahedron Lett.* **1971**, 4835.
(9) Rosowsky, A.; Battaglia, J.; Chen, K.; Modest, E. *J. Org. Chem.* **1968**, *33*, 4288.
(10) Holton, R. A.; Davis, R. G. *Tetrahedron Lett.* **1977**, 533.
(11) Stokker, G. E. *J. Heterocycl. Chem.* **1984**, *21*, 609.
(12) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Table I. Effect of Substitution on Phenyl Ring



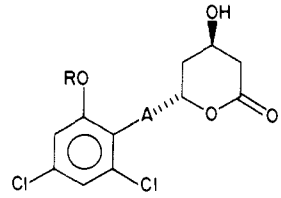
no.	R^2	R^3	R^4	R^5	R^6	recryst solvent	mp, °C	formula[a]	IC_{50},[b] μM	rel potency[c]
24	H	H	H	H	H	*n*-BuCl	97-99	$C_{13}H_{14}O_3$	284	0.004
25	H	H		H	H	acetone	148-150	$C_{19}H_{18}O_3$	55	
26		H	H	H	H	Et_2O	90-92	$C_{19}H_{18}O_3$	3.0	0.63
27	Cl	H	H	H	H	acetone/hexane	129-131	$C_{13}H_{13}ClO_3$	7.4	0.15
28	Cl	H	H	H	Cl	*n*-BuCl	102-104	$C_{13}H_{12}Cl_2O_3$	7.9	0.14
29	Cl	H	Cl	H	H	acetone/hexane	146-148	$C_{13}H_{12}Cl_2O_3$	22	0.08
30	Cl	Cl	H	H	H	acetone/hexane	122-123	$C_{13}H_{12}Cl_2O_3$	64.4	0.017
31	H	Cl	Cl	H	H	*n*-BuCl	116-118	$C_{13}H_{12}Cl_2O_3$	35	
32	CH_3	H	CH_3	H	H	*n*-BuCl	108-110	$C_{15}H_{18}O_3$	29.9	
33	Cl	H		H	Cl	*n*-BuCl	136-138	$C_{20}H_{18}Cl_2O_4$	0.45	4
34	Cl	Cl		H	H	*n*-BuCl	169-171	$C_{20}H_{17}Cl_2FO_4$	17	0.12
35	Cl	H		H	Cl	*n*-BuCl	143.5-145	$C_{20}H_{17}Cl_2FO_4$	0.67	2.7
36	H	Cl	H	Cl	OC_5H_{11}	chromat CH_2Cl_2/acetone	oil	$C_{18}H_{22}Cl_2O_4$	13	
37	CH_3	H		H	CH_3	CH_2Cl_2/Et_2O	131-132	$C_{22}H_{24}O_4$	0.62	3.7
38[d]	Cl	H	Cl	H		*n*-BuCl	76-79	$C_{20}H_{20}Cl_2O_4$	0.39	6
39[d]	Cl	H	Cl	H		*n*-BuCl	141-142	$C_{20}H_{19}Cl_2FO_4$	0.17	10

[a] Analytical results are within ±0.4% of the theoretical value. [b] IC_{50} values were determined by using four or five levels of each inhibitor in the assay system described in ref 3. [c] For estimation of relative inhibitory potencies, compactin was assigned a value of 100 and the IC_{50} value of the test compound was compared with that of compactin determined simultaneously. [d] The two-carbon bridge is saturated.

gave another 18-fold increase in potency. Replacement of the phenyl group in **26** with the chloro group gave compound **27** which displayed about one-half of the potency of **26**. Di-ortho-substitution of **24** with chloro groups (**28**) did not improve the potency of **27**, whereas, each of the other dichloro-substituted compounds (**29–31**) had reduced potency. Replacement of the chloro groups in **29** with methyl groups afforded compound **32** of equal potency. The introduction of a benzyloxy group into the dichloro compound **28** enhanced potency (**33**). Analysis of compounds having different substitution patterns showed that the 2,4-dichloro-6-aralkyl (alkyl) ether substitution patern gave compounds with the highest inhibitory potency (e.g., **65** vs. **34** or **35** and **40** vs. **36**).

The effects of altering the structure of the ether moiety in the 2,4-dichloro-6-aralkyl (aryl, alkyl) ether substituted compounds are shown in Table II. The alkyl ethers **17**, **18**, **40–42**, cycloalkyl ether **43**, and phenyl ether **45** are all less potent than benzyl ether **7a(±)**. When the size of the moiety in ether **7a(±)** was increased by replacement of the benzyl moiety with naphthylmethyl (**47**) or diphenylmethyl (**48**) groups, potency was decreased. The heterocyclic methyl ethers **49** and **50** possessed potency similar to that of **7a(±)**, but the more basic pyridylmethyl ethers (**51–53**) displayed reduced potency. Reducing the basicity of the pyridylmethyl ethers **51** and **52** via conversion to the

Table II. Effects of Substitution in the 6-Alkyl (Aryl, Aralkyl) Ether Series



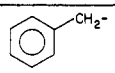
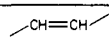
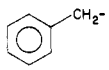
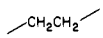
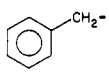
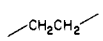
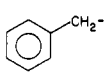
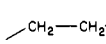
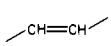
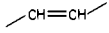
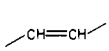
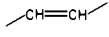
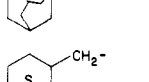
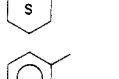
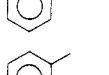
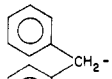
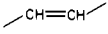
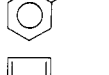
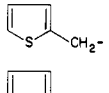
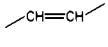
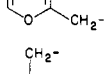
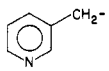
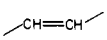
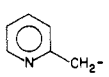
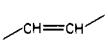
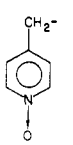
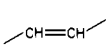
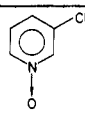
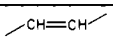
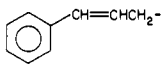
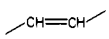
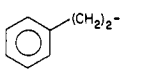
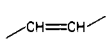
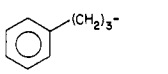
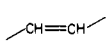
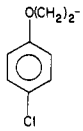
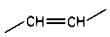
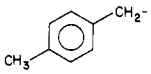
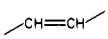
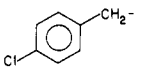
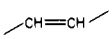
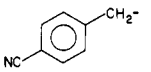
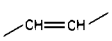
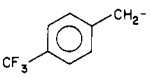
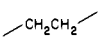
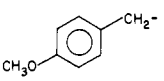
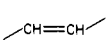
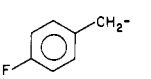
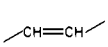
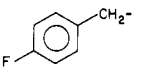
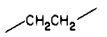
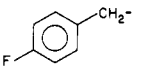
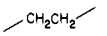
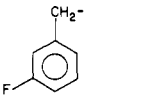
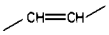
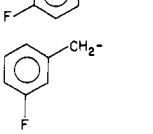
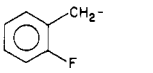
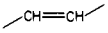
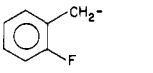
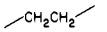
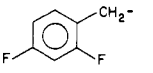
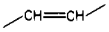
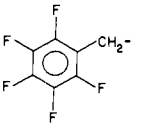
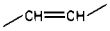
no.	R	A	recryst solvent	mp, °C	formula[a]	IC_{50},[b] μM	rel potency[c]
7a(±)			*n*-BuCl	131-133	$C_{20}H_{18}Cl_2O_4$	0.43	3.5
8a(±)			Et_2O	99-101	$C_{20}H_{20}Cl_2O_4$	0.2	12
8a(+)			*n*-BuCl	108-112	$C_{20}H_{20}Cl_2O_4 \cdot 0.1n\text{-}C_4H_9Cl$	0.068	19.1
8a(−)			*n*-BuCl	104-111	$C_{20}H_{20}Cl_2O_4 \cdot 0.1n\text{-}C_4H_9Cl$	5.2[d]	0.25
17	CH_3SCH_2-		chromat CH_2Cl_2/acetone (9/1)	gum	$C_{15}H_{16}Cl_2O_4S$	0.76	2.1
18	$CH_3O(CH_2)_2OCH_2$-		chromat CH_2Cl_2/acetone (5/1)	gum	$C_{17}H_{20}Cl_2O_6$	11	0.4
22	H		chromat CH_2Cl_2/acetone (4/1)	gum	$C_{13}H_{14}Cl_2O_4$	7.9	0.2
40	C_5H_{11}-		*n*-BuCl/hexane	81-83	$C_{18}H_{22}Cl_2O_4$	1.0	2.4
41	$H_2C{=}CHCH_2$-		chromat CH_2Cl_2/acetone (19/1)	82-84	$C_{16}H_{16}Cl_2O_4$	0.76	3.2
42			chromat CH_2Cl_2/acetone (19/1)	53-66	$C_{22}H_{30}Cl_2O_4$	38	0.09
43			*n*-BuCl	174-176	$C_{25}H_{30}Cl_2O_4$	3.0	0.7
44			*n*-BuCl	154-155	$C_{20}H_{26}Cl_2O_4$	0.75	4.4
45			*n*-BuCl	124-126	$C_{19}H_{16}Cl_2O_4$	1.1	1.4
46			chromat CH_2Cl_2/acetone (5.66/1)	oil	$C_{19}H_{18}Cl_2O_4$	0.33	4.5
47			CH_2Cl_2/hexane	158-160	$C_{24}H_{20}Cl_2O_4$	4.4	0.4
48			*n*-BuCl	135.5-137	$C_{26}H_{22}Cl_2O_4$	6.3	0.7
49			CH_2Cl_2/hexane	129-132	$C_{18}H_{16}Cl_2O_4S$	0.6	3.0
50			CH_2Cl_2/hexane	131-133	$C_{18}H_{16}Cl_2O_5$	0.6	3.0
51			acetone	196.5-197.5	$C_{19}H_{17}Cl_2O_4$	3.7	0.6
52			acetone/Et_2O	152.5-153.5	$C_{19}H_{17}Cl_2NO_4$	3.4	0.6
53			$CHCl_3$	159-160.5	$C_{19}H_{17}Cl_2NO_4$	1.2	1.8
54			THF	131.5-133.5	$C_{19}H_{17}Cl_2NO_5 \cdot 0.25C_4H_8O$	117	0.016

Table II (*Continued*)

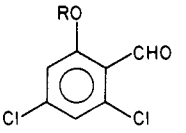
no.	R	A	recryst solvent	mp, °C	formula[a]	IC_{50},[b] μM	rel potency[c]
55			THF	192.5–199.5	$C_{19}H_{17}NO_5$	122	0.016
56			CH_2Cl_2/hexane	120–122	$C_{22}H_{20}Cl_2O_4$	1.9	1.1
57			acetone/hexane	125–126	$C_{21}H_{20}Cl_2O_4$	0.48	5
58			*n*-BuCl	93–94	$C_{22}H_{22}Cl_2O_4$	1.45	1.6
59			acetone/hexane	109–111	$C_{21}H_{19}Cl_3O_5$	1.0	3.3
60			*n*-BuCl	113–118	$C_{21}H_{20}Cl_2O_4$	4.9	0.3
61			*n*-BuCl	111.5–113	$C_{20}H_{17}Cl_3O_4$	2.5	1.7
62			*n*-BuCl	60–65	$C_{21}H_{17}Cl_2NO_4 \cdot 0.1n\text{-}C_4H_9Cl$	2.0	1.25
63			*n*-BuCl	103–105	$C_{21}H_{19}Cl_2F_3O_4$	13	0.16
64			*n*-BuCl	114–115	$C_{21}H_{20}Cl_2O_5$	2.6	0.8
65			*n*-BuCl	125–127	$C_{20}H_{17}Cl_2FO_4$	0.20	7.5
66			*n*-BuCl	151–152	$C_{20}H_{19}Cl_2FO_4$	0.076	38
66(+)			*n*-BuCl/pet. ether	133–135	$C_{20}H_{19}Cl_2FO_4$	0.05	58
67			*n*-BuCl	91.5–92	$C_{20}H_{17}Cl_2FO_4$	0.58	3.4
68			*n*-BuCl	106–115	$C_{20}H_{19}Cl_2FO_4$	0.21	8.0
69			*n*-BuCl	140–142	$C_{20}H_{17}Cl_2FO_4$	0.51	5.9
70			*n*-BuCl	98–100	$C_{20}H_{19}Cl_2FO_4$	0.15	10
71			*n*-BuCl	138–139	$C_{20}H_{16}Cl_2F_2O_4$	0.2	7.5
72			*n*-BuCl	72–75	$C_{20}H_{13}Cl_2F_5O_4 \cdot 0.5n\text{-}C_4H_9Cl$	0.7	2.3

[a] Analytical results are within ±0.4% of the theoretical value. [b] See footnote *b*, Table I. [c] See footnote *c*, Table I. [d] The activity of 8a(−) is probably due to the presence of trace amounts of 8a(+) (threshold = ca. 1%).

corresponding *N*-oxides **54** and **55** failed to enhance potency.

The effects of altering the bridging group between the phenyl and oxygen moieties of **7a(±)** are shown by compounds **56–59**. In each case, lengthening the bridge either diminished or failed to alter potency. Interchanging the

Table III. 6-Substituted 2,4-Dichlorobenzaldehydes



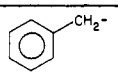
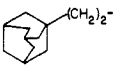
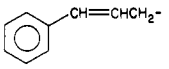
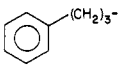
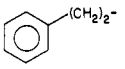
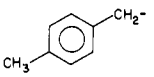
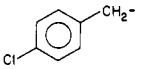
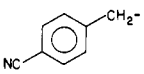
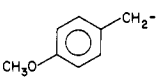
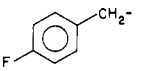
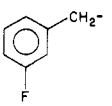
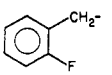
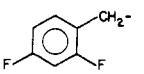
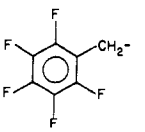
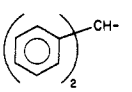
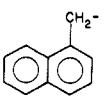
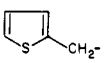
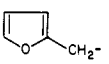
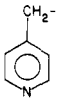
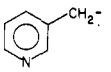
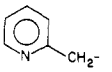
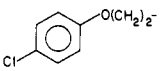
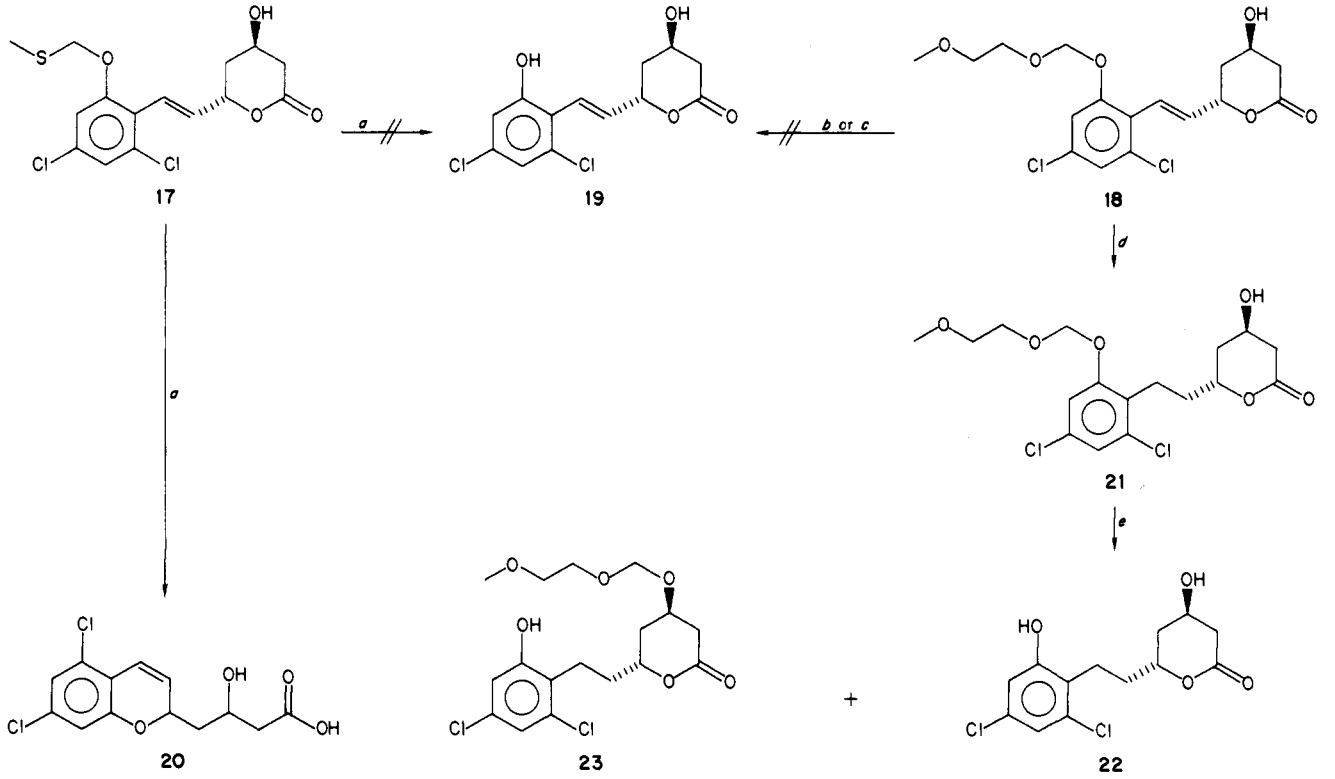
no.	R	recryst solvent	mp, °C	formula	anal.[a]
3		hexane	98–100	$C_{14}H_{10}Cl_2O_2$	C, H
73	C_5H_{11}-	chromat CH_2Cl_2/hexane	oil	$C_{12}H_{14}Cl_2O_2$	*b*
74[c]	CH_3SCH_2-	EtOH/H_2O	75–77	$C_9H_8Cl_2O_2S$	C, H
75	$CH_3O(CH_2)_2OCH_2$-		60–63	$C_{11}H_{12}Cl_2O_4$	*b*, *d*
76	H_2C=$CHCH_2$-	hexane	97–98	$C_{10}H_8Cl_2O_2$	C, H
77	$(CH_3)_3CH_2CH(CH_3)(CH_2)_2$-	chromat (Alumia) CH_2Cl_2/ hexane	oil	$C_{16}H_{22}Cl_2O_2$	*b*
78		hexane	112–114	$C_{19}H_{22}Cl_2O_2$	C, H
79		hexane	99–101	$C_{13}H_8Cl_2O_2$	C, H
80		CH_3CN	109–111	$C_{16}H_{12}Cl_2O_2$	C, H
81				$C_{16}H_{14}Cl_2O_2$	*b*, *d*
82		hexane	96–98	$C_{15}H_{12}Cl_2O_2$	*b*
83		hexane	93–95	$C_{15}H_{12}Cl_2O_2$	C, H
84				$C_{14}H_9Cl_3O_2$	*b*, *d*
85		CH_3CN	179–182	$C_{15}H_9Cl_2NO_2$	C, H, N
86		cyclohexane	95–97	$C_{15}H_{12}Cl_2O_3$	C, H
87		cyclohexane	107–108	$C_{14}H_9Cl_2FO_2$	C, H
88		hexane	108–109.5	$C_{14}H_9Cl_2FO_2$	C, H
89		cyclohexane	101–103	$C_{14}H_9Cl_2FO_2$	C, H
90			127.5–129	$C_{14}H_8Cl_2F_2O_2$	*b*, *d*
91		cyclohexane	120–121.5	$C_{14}H_5Cl_2F_5O_2$	C, H
92		hexane	97–100	$C_{20}H_{14}Cl_2O_2$	C, H
93		toluene	193–195	$C_{18}H_{12}ClO_2$	C, H, Cl
94		hexane	83–85	$C_{12}H_8Cl_2O_2S$	C, H, Cl
95		hexane	65–68	$C_{12}H_8Cl_2O_3$	C, H, Cl

Table III (*Continued*)

no.	R	recryst solvent	mp, °C	formula	anal.[a]
96			145–148	$C_{13}H_9Cl_2NO_2$	*b, d*
97				$C_{13}H_9Cl_2NO_2$	*b, d*
98			120–123	$C_{13}H_9Cl_2NO_2$	*b, d*
99		*n*-BuCl	117–118	$C_{15}H_{11}Cl_3O_3$	*b*

[a] Analysis for the elements indicated were within ±0.4% of the theoretical values. [b] ^1H NMR is in full accord with the proposed structure. [c] Reference 11. [d] Used without purification in the next step.

Scheme III



[a] $HgCl_2$, H_2O, CH_3CN, 80 °C. [b] HBF_4, CH_2Cl_2, 0 °C. [c] $TiCl_4$, CH_2Cl_2, 0 °C. [d] H_2, Rh/C. [e] $ZnBr_2$, CH_2Cl_2.

oxygen and methylene moieties in compounds **8a(±)** and **66** to give compounds **38** and **39** also diminished inhibitory potency.

The results of substitution at the 4-position of the phenyl ring of the benzyl moiety are shown by the data determined for compounds **60–65**. Each of the 4-substituted benzyl ethers had less inhibitory potency than **7a(±)** except the 4-fluorobenzyl ether (**65**), which was twice as potent as the unsubstituted ether. Moving the fluoro group from the para to the meta (**67**) or ortho (**69**) positions diminished potency. The 2,4-difluoro-substituted benzyl ether (**71**) gave potency equal to that of **65** while the pentafluoro-substituted derivative (**72**) had reduced potency. Resolution of **66(±)** afforded **66(+)** which had about 50% of the inhibitory potency of compactin.

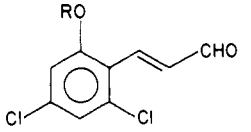
The effect of saturating the ethenyl bridge between the lactone and aromatic moieties is also shown in Table II. In every example, the compound containing the saturated bridge was two-to-four times more potent than its unsaturated analogue.

In conclusion, SAR studies showed that the 2,4-dichloro-6-phenylmethoxy substitution pattern on the aryl ring was necessary for maximum potency. However, substitution on the phenyl ring of the phenylmethoxy substituent was detrimental (except for the fluoro group), while saturation of the (*E*)-ethenyl unit bridging the 5-carbinol moiety and the substituted aryl moiety always increased potency.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solutions were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (rotary evaporator). Proton NMR spectra were recorded in $CDCl_3$, unless noted otherwise, on either a Varian T-60, EM-390, or NT-360 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of the theory unless noted otherwise. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. All

Table IV. 3-(2,4-Dichloro-6-substituted-phenyl)-2-propenals



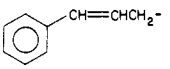
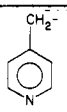
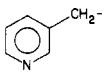
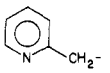
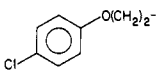
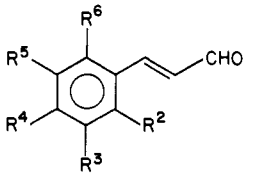
no.	R	recryst solvent	mp, °C	formula[a]	method[b]
4		cyclohexane	110–112	$C_{16}H_{12}Cl_2O$	A
100	C_5H_{11}-	pet. ether	62–64	$C_{14}H_{16}Cl_2O_2$	A
101[c]	CH_3SCH_2-	EtOH/H_2O	104–106	$C_{11}H_{10}Cl_2O_2S$	B
102	$CH_3O(CH_2)_2OCH_2$-	chromat $CHCl_3$/MeOH	oil	$C_{13}H_{14}Cl_2O_4$[d]	B
103	$H_2C{=}CHCH_2$-	hexane	89–90	$C_{12}H_{10}Cl_2O_2$	B
104	$(CH_3)_3CH_2CH(CH_3)(CH_2)_2$-	chromat CH_2Cl/pet. ether	oil	$C_{18}H_{24}Cl_2O_2$	B
105		hexane	127–127.5	$C_{21}H_{24}Cl_2O_2$	B
106		hexane	79–80	$C_{15}H_{10}Cl_2O$	B
107		cyclohexane	112–113	$C_{18}H_{14}Cl_2O_2$	C
108		chromat CH_2Cl_2		$C_{18}H_{16}Cl_2O_2$[d]	B
109		*n*-BuCl	136–139	$C_{17}H_{14}Cl_2O_2$[d]	A
110		chromat CH_2Cl_2/hexane	101–103	$C_{17}H_{14}Cl_2O_2$	B
111		chromat CH_2Cl_2	wax	$C_{16}H_{11}Cl_3O_2$[d]	B
112		chromat CH_2Cl_2		$C_{17}H_{11}Cl_2NO_2$[d]	C
113		*n*-BuCl	123–124	$C_{17}H_{14}Cl_2O_3$	C
114		cyclohexane	122–123	$C_{16}H_{11}Cl_2FO_2$	C
115		*n*-BuCl	100–101.5	$C_{16}H_{11}Cl_2FO_2$	C
116		*n*-BuCl	134–136	$C_{16}H_{11}Cl_2FO_2$	C
117		chromat CH_2Cl_2	125–130	$C_{16}H_{10}Cl_2F_2O_2$[d]	C
118		cyclohexane	108.5–113	$C_{16}H_7Cl_2F_5O_2$[d]	C
119		chromat CH_2Cl_2	oil	$C_{22}H_{16}Cl_2O_2$[d]	B
120		*n*-BuCl	174–177	$C_{20}H_{14}Cl_2O_2$	B
121		*n*-BuCl/hexane	113–115	$C_{14}H_{10}Cl_2O_2S$	B
122		*n*-BuCl/hexane	96–99	$C_{14}H_{10}Cl_2O_3$	B

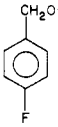
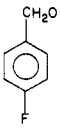
Table IV (*Continued*)

no.	R	recryst solvent	mp, °C	formula[a]	method[b]
123				$C_{15}H_{11}Cl_2O_2$[d]	C
124				$C_{15}H_{11}Cl_2NO_2$[d]	C
125				$C_{15}H_{11}Cl_2NO_2$[d]	C
126		CH_3CN	109-111	$C_{17}H_{13}Cl_3O_3$[d]	A

[a] Analytical results are within ±0.4% of the theoretical values. [b] Methods: (A)[4] CH_3CHO, (B)[5] $C_6H_{11}N{=}CHCH_2Li$, (C)[6] LiCH=CHOEt. [c] See footnote *c*, Table III. [d] No analysis; ^1H NMR are in full accord with the proposed structure.

Table V. 3-(Substituted phenyl)-2-propenals



no.	R^2	R^3	R^4	R^5	R^6	recryst solvent	mp, °C	formula[a]	method[b]
127	Cl	H	H	H	Cl	bp 126-31 (1 mm)	50-55	$C_9H_6Cl_2O$	A
128		H	H	H	H	hexane	73-75	$C_{15}H_{12}O$	*c*
129	CH_3	H	CH_3	H	H	chromat CH_2Cl_2	oil	$C_{11}H_{12}O$[d]	A
130	Cl	H		H	Cl	cyclohexane	75-77	$C_{16}H_{12}Cl_2O_2$	B
131	CH_3	H		H	CH_3	CH_2Cl_2/hexane	65.5-67	$C_{18}H_{18}O_2$	C
132	Cl	Cl		H	H	chromat CH_2Cl_2	142-146	$C_{16}H_{11}Cl_2FO_2$[d]	C
133	Cl	H		H	Cl	CH_3CN	112-114	$C_{16}H_{11}Cl_2FO_2$[d]	C
134	H	Cl	H	Cl	$C_5H_{11}O$-	chromat CH_2Cl_2/hexane	oil	$C_{14}H_{16}Cl_2O_2$	A

[a] Analytical results are within ±0.4% of the theoretical unless otherwise noted. [b] See footnote *b*, Table IV. [c] Prepared by the method of H. Newman: *J. Org. Chem.* 1973, *38*. 2254. [d] No analysis; ^1H NMR are in full accord with the proposed structure.

starting materials were commercially available unless indicated otherwise.

2,4-Dichloro-6-(phenylmethoxy)benzaldehyde (3). Potassium carbonate (9.4 g, 67.8 mmol) was added to a stirred solution of 4,6-dichlorosalicyladehyde (**2**; 10.8 g, 56.5 mmol) in DMF (80 mL). The resulting mixture was stirred at 60 °C for 30 min and treated with benzyl bromide (10.6 g, 62.1 mmol) added dropwise. This mixture was stirred 1 h at 60 °C, cooled to 25 °C, and poured into ice–H_2O (1 L). Collection of the solid gave **3** (15.9 g, 100%) which was recrystallized; NMR δ 5.10 (2 H, s), 7.33 (5 H, s), 10.40 (H, s).

(*E*)-3-[2,4-Dichloro-6-(phenylmethoxy)phenyl]-2-propenal (4) was prepared by the general method of Wollenberg.[8] A 1.37 M solution (24.1 mL, 33 mmol) of *n*-butyllithium in hexane was added cautiously to a stirred solution of *cis*-1-ethoxy-2-(tri-*n*-butylstannyl)ethylene[7] (11.9 g, 33 mmol) in anhydrous THF (75 mL) maintained at −78 °C under a nitrogen atmosphere. The resulting solution was stirred at −78 °C for 1 h and then treated with a solution of **3** (8.4 g, 30 mmol) in anhydrous THF (50 mL). The resulting brown solution was stirred at −78 °C for 1 h and then allowed to warm to 20 °C. The reaction solution was quenched with saturated aqueous $NaHCO_3$ (25 mL), diluted with H_2O (100 mL), and extracted with Et_2O (2 × 200 mL). The organic extracts were combined, washed with brine (2 × 100 mL), dried, filtered, and evaporated to provide the intermediate allylic alcohol as a yellow oil. Allylic rearrangement to the desired product occurred during chromatography on silica gel. Elution with CH_2Cl_2 (200 mL) provided a forerun containing tetrabutyltin which was discarded. Continued elution with CH_2Cl_2/CH_3OH (98:2, v/v; 1500 mL) provided **4** as a pale yellow solid which was recrystallized (6.4 g, 70%); NMR δ 5.10 (2 H, s), 7.33 (5 H, s), 9.68 (H, d).

Methyl (*E*)-7-[2,4-dichloro-6-(phenylmethoxy)phenyl]-5-hydroxy-3-oxo-6-heptenoate (5) was prepared by the general method of Weiler.[8] Methyl acetoacetate (9.56 g, 82.3 mmol) was added dropwise to a stirred suspension of NaH (50% oil sus-

pension) (3.95 g, 82.3 mmol) in anhydrous THF at 0 °C under a nitrogen atmosphere. The resulting solution was stirred 15 min at 0 °C and treated with a 1.6 M solution (51.5 mL, 82.3 mmol) of *n*-butyllithium in hexane added over 5 min. The resulting yellow solution was stirred 15 min at 0 °C and treated with a solution of **4** (25.3 g, 82.3 mmol) in anhydrous THF (150 mL). After the mixture was stirred for 15 min at 0 °C, the resulting orange solution was quenched by dropwise addition of 12 N HCl (ca. 20 mL). The reaction mixture was diluted with H_2O (100 mL) and extracted with Et_2O (3 × 300 mL). The organic extracts were combined, washed with brine (3 × 100 mL), dried, and filtered. The filtrate was evaporated to provide **5** as a yellow oil (34.8 g, 100%); NMR δ 2.75 (2 H, d), 3.45 (2 H, s), 3.72 (3 H, s), 4.71 (H, m), 5.50 (2 H, s), 7.37 (5 H, s).

Methyl (*E*)-7-[2,4-Dichloro-6-(phenylmethoxy)phenyl]-3,5-dihydroxy-6-heptenoate (6). Sodium tetrahydridoborate (1.55 g, 41.1 mmol) was added with stirring to a cooled solution (5 °C) of **5** (34.8 g, 82.3 mmol) in EtOH (200 mL) at a rate sufficient to maintain the internal temperature at 15–20 °C. The resulting solution was stirred with ice-bath cooling for 15 min, cautiously acidified with 6 N HCl, diluted with H_2O (500 mL), and extracted with Et_2O (3 × 250 mL). The organic extracts were combined, washed with brine (4 × 100 mL), dried, and filtered. The filtrate was evaporated in vacuo to provide **6** as a yellow oil (34.8 g, 99.5%); NMR δ 2.45 (2 H, d), 3.65 (3 H, s), 4.18 (H, m), 4.45 (H, m), 4.98 (2 H, s), 7.28 (5 H, s).

(*E*)-6-[2-[2,4-Dichloro-6-(phenylmethoxy)phenyl]-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (7a(±) and 7b(±)). A solution of **6** (34.8 g, 81.8 mmol), 1 N NaOH (82 mL, 82 mmol), and EtOH (200 mL) was stirred at 25 °C for 15 min. The reaction solution was acidified with 6 N HCl, diluted with H_2O (400 mL), and extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with brine (3 × 100 mL), dried, and filtered. The filtrate was evaporated to provide the crude acid mixture as an orange oil (33.3 g, 99%); NMR δ 2.47 (2 H, d), 4.30 (2 H, br m), 4.98 (2 H, s), 7.30 (5 H, s).

A solution of the crude acid mixture (33.3 g, 81.3 mmol) in toluene (300 mL) was heated at reflux in a Dean–Stark apparatus. After 2 h the Dean–Stark apparatus was replaced with a Soxhlet containing 3-Å molecular sieves (100 g). Heating at reflux was continued for an additional 4 h and then the toluene was removed in vacuo, leaving a mixture of **7a(±)** and **7b(±)** as a yellow oil (31.7 g). The oil was chromatographed on silica gel (900 g). Elution with CH_2Cl_2/acetone (9:1, v/v; 4000 mL) provided a forerun which was discarded. Continued elution with the same eluant (500 mL) gave the trans isomer **7a(±)** as a pale yellow solid (5.8 g). Further elution with the same eluant (3250 mL) gave a mixture of **7a(±)** and **7b(±)** as a tan solid (8.8 g). This mixture was chromatographed on a Waters Prep LC500 instrument. Separation of this mixture was accomplished by using two prep PAK-500/silica cartridges in series and eluting with CH_2Cl_2/acetone (9:1, v/v). Using the shave–recycle technique, another 3.3 g of **7a(±)** and 4.7 g of the cis isomer **7b(±)** were obtained.

The fractions of **7a(±)** were combined and recrystallized to give an analytical sample (7.3 g, 23%); NMR δ 1.85 (H, d), 1.85 (H, m), 2.02 (H, m), 2.60 (H, m), 2.75 (H, dd), 4.30 (H, m), 5.08 (2 H, s), 5.29 (H, m), 6.52 (H, dd), 6.79 (H, dd), 6.90 (H, d), 7.05 (H, d), 7.44 (5 H, m).

The cis isomer **7b(±)** was recrystallized from *n*-BuCl to provide an analytical sample (4.3 g, 13%), mp 130–131.5 °C; NMR δ 1.70 (H, m), 2.00 (H, d), 2.32 (H, m), 2.48 (H, dd), 2.94 (H, m), 4.29 (H, m), 4.82 (H, m), 5.09 (2 H, s), 6.57 (H, dd), 6.80 (H, dd), 6.85 (H, d), 7.07 (H, d), 7.43 (5 H, m). Anal. ($C_{20}H_{18}Cl_2O_4$) H, C: calcd, 61.08; found, 61.55.

The coupling constants of the lactone C-4 protons and the chemical shifts of the C-6 protons were used for the structural assignments of **7a(±)** and **7b(±)**. The equatorial coupling constants of the C-4 proton of **7a(±)** were 5.2, 5.0, 4.5, 3.3, and 3.0 compared to 9.2, 8.0, 5.9, 5.2, and 4.4 for the axial coupling constants of the C-4 proton of **7b(±)**. The axial hydroxyl group of **7a(±)** deshields the C-6 proton by 0.47 ppm from the chemical shift assigned to the corresponding proton of **7b(±)**. The tabulation of the coupling constants for the protons of the lactone ring is included in the supplementary material.

***trans*-6-[2-[2,4-Dichloro-6-(phenylmethoxy)phenyl]-ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (8a(±)).** A solution of **7a(±)** (1.1 g, 28 mmol) in THF (50 mL) was magnetically stirred and hydrogenated at room temperature and atmospheric pressure in the presence of 5% rhodium-on-carbon (110 mg) until 1.5 molar equiv of hydrogen had been consumed. After removal of the catalyst by filtration, the filtrate was evaporated in vacuo to provide **8a(±)** as a pale yellow oil. The oil was chromatographed on a silica gel column (200 g). Elution with acetone/CH_2Cl_2 (1:9, v/v; 560 mL) provided a forerun which was discarded. Continued elution with the same eluant (240 mL) gave **8a(±)** as a colorless oil which solidified upon trituration with ether. Recrystallization provided the analytical sample as colorless needles (0.67 g, 61%); NMR δ 1.83 (4 H, m), 2.60 (2 H, m), 2.90 (2 H, m), 4.30 (H, m), 4.62 (H, m), 5.05 (2 H, s), 7.42 (5 H, s).

Resolution of (±)-*trans*-(*E*)-6-[2-[2,4-Dichloro-6-(phenylmethoxy)phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (8a(±)). A solution of **8a(±)** (1.75 g, 4.4 mmol) in *l*-(−)-α-methylbenzylamine (10 mL) was stirred for 18 h at ambient temperature and then poured into H_2O (50 mL). The aqueous mixture was acidified with 6 N HCl and the resulting solid was collected and suspended in Et_2O/CH_2Cl_2 (1:1, v/v; 200 mL). The insoluble solid was collected and recrystallized from 2-propanol to give diastereomer A (0.8 g) as colorless needles, mp 177–179 °C; NMR δ 1.43 (3 H, d, J = 7 Hz), 2.20 (2 H, d, J = 7 Hz), 2.80 (2 H, m), 3.82 (H, m), 4.12 (H, m), 5.05 (2 H, s), 6.81 (H, d, J = 2 Hz), 7.00 (H, d, J = 2 Hz), 7.20–7.43 (10 H, m). Anal. ($C_{28}H_{31}Cl_2NO_4$) C, H, N.

The Et_2O/CH_2Cl_2 filtrate was dried and evaporated in vacuo to provide crude diastereomer B as a viscous oil. The oil was purified by flash chromatography on silica gel. Elution with acetone/CH_2Cl_2 (1:4, v/v; 800 mL) gave a forerun which was discarded. Continued elution with the same eluant provided a solid which was recrystallized from *n*-BuCl/petroleum ether to give diastereomer B (0.9 g) as an amphorous solid, mp 130–132 °C; NMR δ 1.43 (3 H, d, J = 7 Hz), 2.20 (2 H, d, J = 2 Hz), 2.82 (H, m), 3.73 (H, m), 4.10 (H, m), 5.04 (2 H, s), 6.86 (H, d, J = 2 Hz), 7.03 (H, d, J = 2 Hz), 7.23–7.43 (10 H, m). Anal. ($C_{28}H_{31}Cl_2NO_4$) C, H, N.

(+)-*trans*-(*E*)-6-[2-[2,4-Dichloro-6-(phenylmethoxy)-phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (8a(+)). Diastereomer A (0.78 g, 1.5 mmol) was dissolved in 95% EtOH (50 mL) containing 1 N NaOH (3.0 mL, 3.0 mmol). The resulting solution was heated at reflux for 18 h. The solvent was removed in vacuo, leaving a residue which was mixed with H_2O and acidified with 6 N HCl. The resulting mixture was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried, and filtered. The filtrate was evaporated, leaving the intermediate acid as a yellow semisolid (0.6 g). A solution of the semisolid in toluene (150 mL) was heated at reflux with a Soxhlet containing molecular sieves (3 Å) for 6 h. The solution was evaporated and the solid was purified by flash chromatography on silica gel. Elution with acetone/CH_2Cl_2 (1:4, v/v) gave the lactone **8a(+)** as a solid which was recrystallized to provide colorless clusters (0.33 g); $[\alpha]^{25}_D$ +16.6° (c 1.0, $CHCl_3$); NMR δ 2.60 (2 H, m), 2.93 (2 H, m), 4.30 (H, m), 4.70 (H, m), 5.06 (2 H, s), 6.83 (H, d, J = 2 Hz), 7.02 (H, d, J = 2 Hz), 7.30–7.50 (5 H, m).

(−)-*trans*-(*E*)-6-[2-[2,4-Dichloro-6-(phenylmethoxy)-phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (8a(−)). A solution of diastereomer B (0.78 g, 1.5 mmol) in 95% EtOH (20 mL) containing 1 N NaOH (3 mL, 3.0 mmol) was heated at reflux for 42 h. Use of the same workup, lactonization, and purification described for **8a(+)** gave **8a(−)** as a solid. Recrystallization provided colorless clusters (0.26 g); $[\alpha]^{25}_D$ −17.7, (c 1.0, $CHCl_3$); NMR δ 2.60 (2 H, m), 2.93 (2 H, m), 4.30 (H, m), 4.70 (H, m), 5.06 (2 H, s), 6.83 (H, d, J = 2 Hz), 7.02 (H, d, J = 2 Hz), 7.3–7.50 (5 H, m).

The optical purities of **8a(+)** and **8a(−)** were determined by NMR with use of ca. 0.5 molar equiv of $Eu(hfc)_3$ in $CDCl_3$; each enantiomer was found to be free of the other enantiomer within the limits of detection (threshold = ca. 1%). Therefore, the optical purity of **8a(+)** and **8a(−)** was estimated to be 99 ± 1%.

5,7-Dichloro-3,4-dihydro-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]naphthalene (10). A solution of **9**[9] (16.2 g, 75 mmol) in dry THF (80 mL) was added to a rapidly stirred solution of LDA prepared from diisopropylamine (11.9 mL, 82.5 mmol) and *n*-butyllithium (82.5 mmol) in dry THF (200 mL) and

HMPA (25 mL) at −78 °C under an atmosphere of N_2. After an additional 3 min at −78 °C, *tert*-butyldimethylsilyl chloride (12.4 g, 82.5 mmol) was added and the cooling bath was removed. The reaction mixture was stirred at ambient temperature for 0.5 h before being quenched by the addition of Et_2O (300 mL) and H_2O (300 mL). The Et_2O layer was separated and washed with H_2O (2 × 200 mL), dried, filtered, and evaporated to yield **10** (22.4 g, 90%) as a light yellow oil; NMR δ 0.2 (6 H, s), 0.95 (9 H, s), 2.35 (2 H, t, J = 9 Hz), 2.96 (2 H, t, J = 9 Hz), 5.6 (H, s), 6.75 (H, d, J = 2 Hz), 7.05 (H, d, J = 2 Hz).

3-[2,4-Dichloro-6-(hydroxymethyl)phenyl]propanoic Acid (11). Ozone was bubbled into a stirred solution of **10** (22.4 g, 68 mmol) in CH_2Cl_2 (250 mL) and CH_3OH (250 mL) at −78 °C until the color of the solution turned blue (ca. 30 min). After the excess ozone was purged by bubbling N_2 through the solution, $NaBH_4$ (2.85 g, 75 mmol) was added and the reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was then evaporated at <30 °C, diluted with 0.1 N HCl (750 mL), and stirred vigorously at 20 °C before filtration. Trituration of the sticky solid with hexane and subsequent crystallization from HOAc–H_2O provided **11** (10.9 g, 64%), mp 161–163 °C, as colorless needles. Recrystallization from HOAc–H_2O afforded an analytical sample, mp 166–167 °C; NMR (Me_2SO) δ 2.3–2.6 (2 H, m), 2.8–3.1 (2 H, m), 4.6 (2 H, s), 5.4 (H, br s), 7.4–7.5 (2 H, m), 12.3 (H, br s). Anal. ($C_{10}H_{10}Cl_2O_3$) C, H.

Methyl 3-[2,4-Dichloro-6-(hydroxymethyl)phenyl]propanoate (12). A solution of **11** (9.6 g, 38.5 mmol) in DMF (100 mL) containing $NaHCO_3$ (3.7 g, 44 mmol) was stirred at 55–60 °C for 0.5 h and then treated with methyl iodide (4.8 mL, 80 mmol). After stirring and heating for an additional 1.5 h, the reaction mixture was cooled and distributed between Et_2O (300 mL) and H_2O (800 mL). The Et_2O layer was washed with H_2O (2 × 200 mL), dried, filtered, and evaporated to afford **12** (8.8 g, 87%) as a brown oil; NMR δ 2.5–2.75 (2 H, m), 2.95–3.2 (2 H, m), 3.25 (H, br s), 3.7 (3 H, s), 4.7 (2 H, s), 7.33 (2 H, s).

Methyl 3-[2,4-Dichloro-6-(chloromethyl)phenyl]propanoate (13). An intimate mixture of **12** (8.8 g, 33.5 mmol) and thionyl chloride (5 mL, 70 mmol) was refluxed gently for 2.5 h. Evaporation of the excess thionyl chloride under vacuum provided **13** (9.2 g, 97%) as a brown oil; NMR δ 2.5–2.7 (2 H, m), 3.0–3.3 (2 H, m), 3.65 (3 H, s), 4.55 (2 H, s), 7.23 (H, d, J = 1 Hz), 7.33 (H, d, J = 1 Hz).

Methyl 3-[2,4-Dichloro-6-[(4-fluorophenoxy)methyl]phenyl]propanoate (14). Powdered sodium 4-fluorophenoxide (1.41 g, 10.5 mmol) was added to a solution of **13** (2.9 g, 10.3 mmol) in DMF (20 mL) and the mixture was stirred at 50–60 °C for 0.5 h. The reaction mixture was cooled, diluted with H_2O (200 mL), and extracted with Et_2O (3 × 100 mL). The Et_2O extracts were combined and washed with H_2O (3 × 200 mL), dried, filtered, and evaporated. The residual brown oil was chromatographed on silica gel using CH_2Cl_2/hexane (1:1, v/v) as eluant to give **14** (2 g, 54%); NMR δ 2.55–2.75 (2 H, m), 3.0–3.3 (2 H, m), 3.65 (3 H, s), 5.03 (2 H, s), 6.8–7.4 (6 H, m).

3-[2,4-Dichloro-6-[(4-fluorophenoxy)methyl]phenyl]propanol (15). A solution of **14** (2 g, 5.6 mmol) in Et_2O (25 mL) was added dropwise to a stirred suspension of LAH (139 mg, 3.65 mmol) in Et_2O (10 mL) under a N_2 atmosphere. After stirring for 15 min, the reaction mixture was cooled to 0 °C and worked up by the sequential addition of H_2O (0.14 mL), 20% NaOH (0.11 mL), and H_2O (0.41 mL). After the mixture was stirred for 0.5 h at 20 °C, anhydrous $MgSO_4$ was added and the mixture was filtered and evaporated to yield **15** (1.6 g, 87%), mp 95–96 °C, as a white powder. Recrystallization from *n*-BuCl–hexane gave an analytical sample, mp 95.5–96.5 °C; NMR δ 1.65–1.95 (2 H, m), 2.7–2.95 (2 H, m), 3.55–3.75 (2 H, m), 5.0 (2 H, s), 6.8–7.4 (6 H, m).

3-[2,4-Dichloro-6-[(4-fluorophenoxy)methyl]phenyl]propanal (16). A solution of **15** (1.5 g, 4.6 mmol) in CH_2Cl_2 (10 mL) was added rapidly to a suspension of pyridinium chlorochromate (1.46 g, 6.8 mmol) in CH_2Cl_2 (10 mL) at 20 °C. After stirring for 2 h, the reaction mixture was diluted with Et_2O (30 mL) and filtered through silica gel (40 g). The black residue in the reaction vessel was washed with Et_2O (3 × 50 mL) and each fraction was filtered through silica gel. The clear, pale tan filtrates were combined and evaporated to give **16** (1.4 g, 93%) as a light brown oil; NMR δ 2.65–2.9 (2 H, m), 2.95–3.2 (2 H, m), 5.0 (2 H, s), 6.75–7.4 (6 H, m), 9.85 (H, s).

4-(5,7-Dichloro-2*H*-benzopyran-2-yl)-2-hydroxybutyric Acid (20). The MTM ether **17** was cleaved by the general method of Holton.[10] $HgCl_2$ (1.5 g, 5.5 mol) was added to a solution of the MTM ether **17** (1.3 g, 4.3 mmol) in CH_3CN (20 mL) containing H_2O (5 mL). After refluxing for 9 h, the mixture was cooled to ambient temperature and diluted with Et_2O (100 mL). The ether layer was separated, washed with H_2O (3 × 100 mL), dried, and evaporated to give a viscous oil (0.9 g). The oil was flash chromatographed on a 5 × 15 cm column of silica gel (230–400 mesh). Elution with acetic acid/CH_2Cl_2 (1:19, v/v; 700 mL) provided a forerun which was discarded. Continued elution with the same eluant (450 mL) gave **20** as a viscous oil (650 mg, 50%); NMR δ 1.67–2.17 (2 H, m), 2.56 (2 H, m), 4.37 (H, m), 5.10 (H, m), 5.8 (H, m), 6.73 (H, m), 6.90 (H, m), 7.16 (H, m). Anal. ($C_{13}H_{12}Cl_2O_4$) H; C: calcd, 51.51; found, 52.12.

***trans*-6-[2-[2,4-Dichloro-6-[(methoxyethoxy)methoxy]phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (21)** was prepared from **18** (800 mg, 2 mmol) by the procedure used to synthesize **8a(±)** and purified by chromatography to provide a colorless oil (500 mg); NMR δ 3.36 (3 H, s), 3.57 (2 H, m), 3.80 (2 H, m), 4.37 (H, m), 4.70 (H, m), 5.23 (2 H, s), 7.37 (2 H, m). Compound **21** was used to prepare **22** without further purification.

***trans*-6-[2-(2,4-Dichloro-6-hydroxyphenyl)ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (22).** The MEM ether group of **21** was removed by the general procedure of Corey.[12] $ZnBr_2$ (2 g, 8.9 mmol) was added to a magnetically stirred solution of MEM ether (650 mg, 1.7 mmol) **21** in CH_2Cl_2 (8 mL). After 1.5 h another 2 g of $ZnBr_2$ was added and stirring was continued for another 0.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (50 mL), diluted with Et_2O (150 mL), and acidified with 12 N HCl. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The organic extracts were combined, washed with H_2O (2 × 50 mL), dried, and evaporated to give a yellow gum. The gum was flash chromatographed on a 5 × 15 cm column of silica gel (230–400 mesh). Elution with acetone/CH_2Cl_2 (1:4, v/v; 370 mL) provided a mixture of **21** and **23** (150 mg). Continued elution with the same eluant (350 mL) gave the lactone **22** as a colorless gum (140 mg, 27%); NMR δ 2.70 (2 H, m), 4.40 (H, m), 4.68 (H, m), 6.80 (H, d, J = 2 Hz), 6.96 (H, d, J = 2 Hz). The mixture of **21** and **23** was rechromatographed on a 3 × 15 cm column of silica gel (230–400 mesh). Elution with acetone/CH_2Cl_2 (1:6, v/v; 140 mL) provided **23** as a gum (70 mg); NMR δ 3.37 (3 H, s), 3.47–3.87 (4 H, m), 4.17 (H, m), 4.70 (H, m), 4.73 (2 H, s), 6.77 (H, d, J = 2 Hz), 6.87 (H, d, J = 2 Hz); MS, m/e 292 (M^+).

***trans*-6-[2-[2,4-Dichloro-6-[[4-(trifluoromethyl)phenyl]methoxy]phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (63).** This product was prepared analogously to **3** with **22** (130 mg, 0.43 mmol) as the starting material and purified by chromatography followed by recrystallization; NMR δ 2.65 (2 H, m), 4.33 (H, m), 4.70 (H, m), 5.13 (2 H, s), 6.8 (H, d, J = 2 Hz), 7.06 (H, d, J = 7 Hz), 7.66 (4 H, m); ^{19}F NMR ($CFCl_3$) δ −6.20 (s).

Isolation of HMG-CoA Reductase. Carried out as previously described.[3]

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Supplementary Material Available: A tabulation of the chemical shifts and coupling constants for the lactone protons of **7a(±)** and **7b(±)** (1 page). Ordering information is given on any current masthead page.