

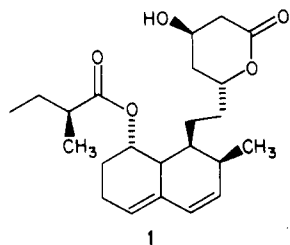
## 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 2. Structural Modification of 7-(Substituted aryl)-3,5-dihydroxy-6-heptenoic Acids and Their Lactone Derivatives

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Received May 2, 1985

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<sup>1</sup> and biological activity<sup>2</sup> 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<sup>3</sup> 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).



**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<sub>2</sub>CO<sub>3</sub> and are listed

in Table III. The general methods of Baker<sup>4</sup> (A), Wittig<sup>5</sup> (B), and Wollenberg<sup>6</sup> (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<sub>2</sub>O) 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<sub>2</sub> 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

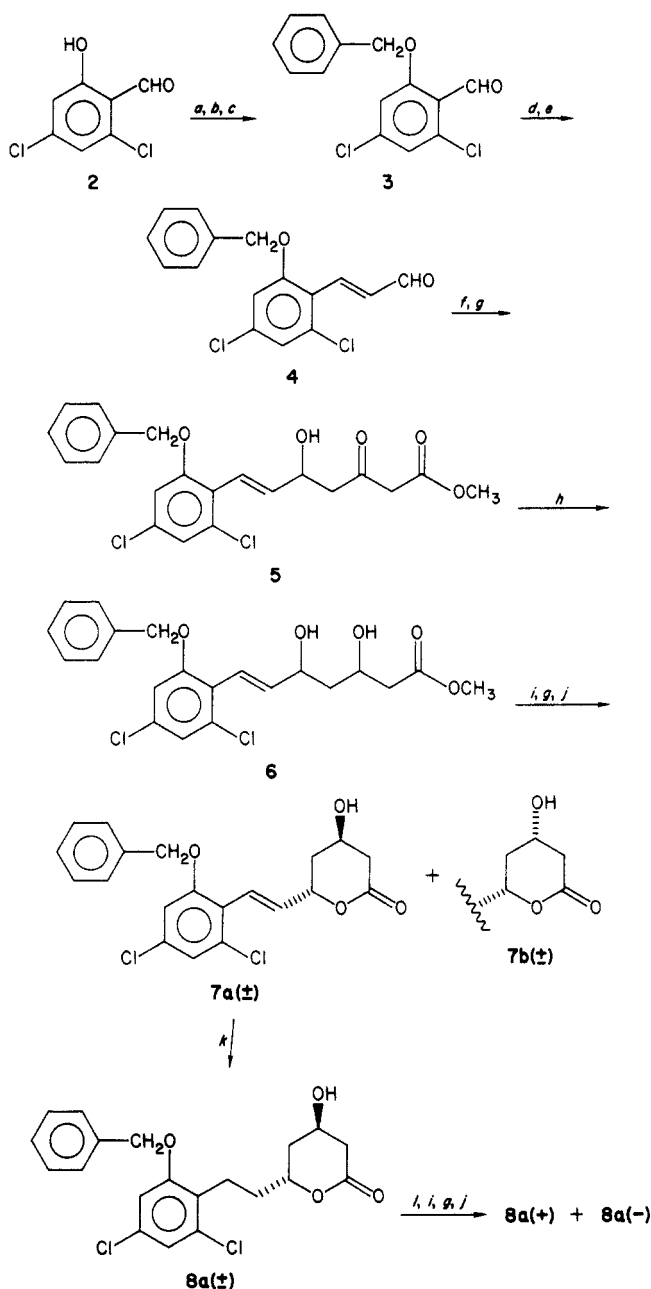
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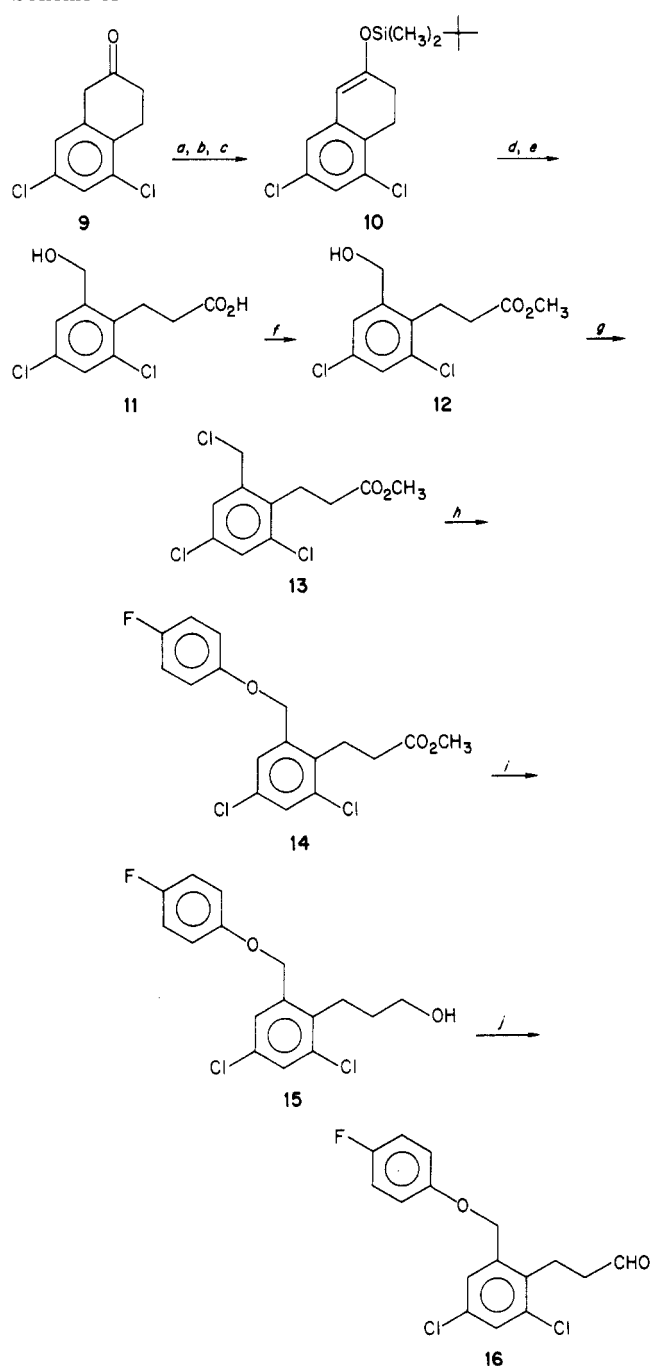
Scheme I



<sup>a</sup>K<sub>2</sub>CO<sub>3</sub>. <sup>b</sup>C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>Br. <sup>c</sup>DMF. <sup>d</sup>LiCH=CHOC<sub>2</sub>H<sub>5</sub>. <sup>e</sup>Silica gel. <sup>f</sup>CH<sub>2</sub>COCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>. <sup>g</sup>H<sup>+</sup>. <sup>h</sup>NaBH<sub>4</sub>, EtOH. <sup>i</sup>OH<sup>-</sup>. <sup>j</sup>C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>, Δ. <sup>k</sup>H<sub>2</sub>, Rh/C. <sup>l</sup>/(-)-C<sub>6</sub>H<sub>5</sub>CH(CH<sub>3</sub>)NH<sub>2</sub>.

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<sup>10</sup> gave the butyric acid derivative 20. A similar ring closure was observed previously when propenal 101 was treated under identical conditions.<sup>11</sup> If the ethylene bridge of 18 was first reduced (21), the MEM ether could be cleaved using Corey's<sup>12</sup>

Scheme II



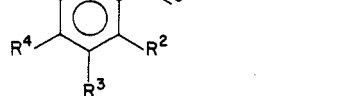


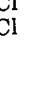





<sup>a</sup>LDA, -78 °C. <sup>b</sup>HMPA. <sup>c</sup>*t*-BuSiMe<sub>2</sub>Cl. <sup>d</sup>O<sub>3</sub>, MeOH, -78 °C. <sup>e</sup>NaBH<sub>4</sub>. <sup>f</sup>CH<sub>3</sub>I, DMF, NaHCO<sub>3</sub>. <sup>g</sup>SOCl<sub>2</sub>. <sup>h</sup>4-F<sub>2</sub>C<sub>6</sub>H<sub>4</sub>O<sup>-</sup>Na<sup>+</sup>, DMF. <sup>i</sup>LAH, Et<sub>2</sub>O. <sup>j</sup>Pyridinium chlorochromate, CH<sub>2</sub>Cl<sub>2</sub>.

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

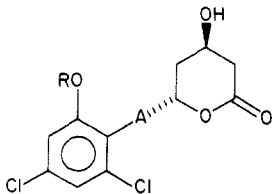
The ring-opened sodium dihydroxycarboxylate forms of the compounds listed in Tables I and II were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase. The results of substitution on the phenyl ring are shown in Table I. Monosubstitution of the phenyl ring 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)

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no.	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	recryst solvent	mp, °C	formula <sup>a</sup>	IC <sub>50</sub> , <sup>b</sup> μM	rel potency <sup>c</sup>
24	H	H	H	H	H	<i>n</i> -BuCl	97-99	C <sub>13</sub> H <sub>14</sub> O <sub>3</sub>	284	0.004
25	H	H		H	H	acetone	148-150	C <sub>19</sub> H <sub>18</sub> O <sub>3</sub>	55	
26		H	H	H	H	Et <sub>2</sub> O	90-92	C <sub>19</sub> H <sub>18</sub> O <sub>3</sub>	3.0	0.63
27	Cl	H	H	H	H	acetone/hexane	129-131	C <sub>13</sub> H <sub>13</sub> ClO <sub>3</sub>	7.4	0.15
28	Cl	H	H	H	Cl	<i>n</i> -BuCl	102-104	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub>	7.9	0.14
29	Cl	H	Cl	H	H	acetone/hexane	146-148	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub>	22	0.08
30	Cl	Cl	H	H	H	acetone/hexane	122-123	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub>	64.4	0.017
31	H	Cl	Cl	H	H	<i>n</i> -BuCl	116-118	C <sub>13</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub>	35	
32	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	<i>n</i> -BuCl	108-110	C <sub>15</sub> H <sub>18</sub> O <sub>3</sub>	29.9	
33	Cl	H		H	Cl	<i>n</i> -BuCl	136-138	C <sub>20</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>4</sub>	0.45	4
34	Cl	Cl		H	H	<i>n</i> -BuCl	169-171	C <sub>20</sub> H <sub>17</sub> Cl <sub>2</sub> FO <sub>4</sub>	17	0.12
35	Cl	H		H	Cl	<i>n</i> -BuCl	143.5-145	C <sub>20</sub> H <sub>17</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.67	2.7
36	H	Cl	H	Cl	OC <sub>5</sub> H <sub>11</sub>	chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone	oil	C <sub>18</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>4</sub>	13	
37	CH <sub>3</sub>	H		H	CH <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> /Et <sub>2</sub> O	131-132	C <sub>22</sub> H <sub>24</sub> O <sub>4</sub>	0.62	3.7
38 <sup>d</sup>	Cl	H	Cl	H		<i>n</i> -BuCl	76-79	C <sub>20</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	0.39	6
39 <sup>d</sup>	Cl	H	Cl	H		<i>n</i> -BuCl	141-142	C <sub>20</sub> H <sub>19</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.17	10

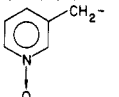
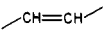
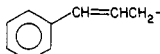
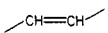
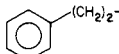
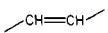
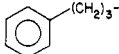
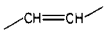
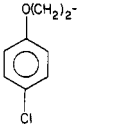
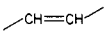
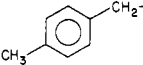
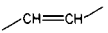
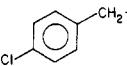
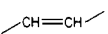
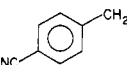
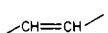
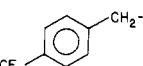
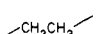
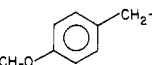
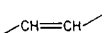
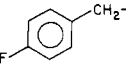
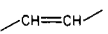
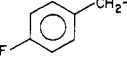
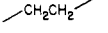
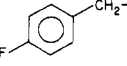
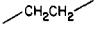
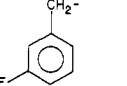
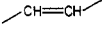
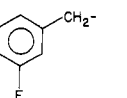
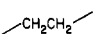
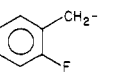
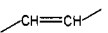
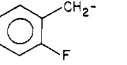
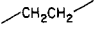
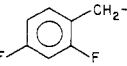
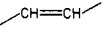
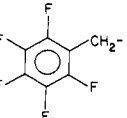
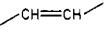
The effects of altering the structure of the ether moiety in the 2,4-dichloro-6-aralkyl (aryl, alkyl) ether substituted compounds are shown in Table II. The alkyl ethers 17, 18, 40–42, cycloalkyl ether 43, and phenyl ether 45 are all less potent than benzyl ether 7a(±). When the size of the moiety in 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 <sup>a</sup>	IC <sub>50</sub> , <sup>b</sup> μM	rel potency <sup>c</sup>
7a(±)			<i>n</i> -BuCl	131-133	C <sub>20</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>4</sub>	0.43	3.5
8a(±)			Et <sub>2</sub> O	99-101	C <sub>20</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	0.2	12
8a(+)			<i>n</i> -BuCl	108-112	C <sub>20</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub> · 0.1 <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl	0.068	19.1
8a(-)			<i>n</i> -BuCl	104-111	C <sub>20</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub> · 0.1 <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl	5.2 <sup>d</sup>	0.25
17	CH <sub>3</sub> SCH <sub>2</sub> -		chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (9/1)	gum	C <sub>15</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>4</sub> S	0.76	2.1
18	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -		chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (5/1)	gum	C <sub>17</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>6</sub>	11	0.4
22	H		chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (4/1)	gum	C <sub>13</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>4</sub>	7.9	0.2
40	C <sub>5</sub> H <sub>11</sub> -		<i>n</i> -BuCl/hexane	81-83	C <sub>18</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>4</sub>	1.0	2.4
41	H <sub>2</sub> C=CHCH <sub>2</sub> -		chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (19/1)	82-84	C <sub>16</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>4</sub>	0.76	3.2
42	(CH <sub>3</sub> ) <sub>3</sub> CCH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> -		chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (19/1)	53-66	C <sub>22</sub> H <sub>30</sub> Cl <sub>2</sub> O <sub>4</sub>	38	0.09
43			<i>n</i> -BuCl	174-176	C <sub>25</sub> H <sub>30</sub> Cl <sub>2</sub> O <sub>4</sub>	3.0	0.7
44			<i>n</i> -BuCl	154-155	C <sub>20</sub> H <sub>26</sub> Cl <sub>2</sub> O <sub>4</sub>	0.75	4.4
45			<i>n</i> -BuCl	124-126	C <sub>19</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>4</sub>	1.1	1.4
46			chromat CH <sub>2</sub> Cl <sub>2</sub> / acetone (5.66/1)	oil	C <sub>19</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>4</sub>	0.33	4.5
47			CH <sub>2</sub> Cl <sub>2</sub> /hexane	158-160	C <sub>24</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	4.4	0.4
48			<i>n</i> -BuCl	135.5-137	C <sub>26</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>4</sub>	6.3	0.7
49			CH <sub>2</sub> Cl <sub>2</sub> /hexane	129-132	C <sub>18</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>4</sub> S	0.6	3.0
50			CH <sub>2</sub> Cl <sub>2</sub> /hexane	131-133	C <sub>18</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>5</sub>	0.6	3.0
51			acetone	196.5-197.5	C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> O <sub>4</sub>	3.7	0.6
52			acetone/Et <sub>2</sub> O	152.5-153.5	C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> NO <sub>4</sub>	3.4	0.6
53			CHCl <sub>3</sub>	159-160.5	C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> NO <sub>4</sub>	1.2	1.8
54			THF	131.5-133.5	C <sub>19</sub> H <sub>17</sub> Cl <sub>2</sub> NO <sub>5</sub> · 0.25C <sub>4</sub> H <sub>8</sub> O	117	0.016

Table II (Continued)

no.	R	A	recryst solvent	mp, °C	formula <sup>a</sup>	IC <sub>50</sub> <sup>b</sup> μM	rel potency <sup>c</sup>
55			THF	192.5-199.5	C <sub>19</sub> H <sub>17</sub> NO <sub>3</sub>	122	0.016
56			CH <sub>2</sub> Cl <sub>2</sub> /hexane	120-122	C <sub>22</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	1.9	1.1
57			acetone/hexane	125-126	C <sub>21</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	0.48	5
58			<i>n</i> -BuCl	93-94	C <sub>22</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>4</sub>	1.45	1.6
59			acetone/hexane	109-111	C <sub>21</sub> H <sub>19</sub> Cl <sub>3</sub> O <sub>5</sub>	1.0	3.3
60			<i>n</i> -BuCl	113-118	C <sub>21</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>4</sub>	4.9	0.3
61			<i>n</i> -BuCl	111.5-113	C <sub>20</sub> H <sub>17</sub> Cl <sub>3</sub> O <sub>4</sub>	2.5	1.7
62			<i>n</i> -BuCl	60-65	C <sub>21</sub> H <sub>17</sub> Cl <sub>2</sub> NO <sub>4</sub> · 0.1 <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl	2.0	1.25
63			<i>n</i> -BuCl	103-105	C <sub>21</sub> H <sub>19</sub> Cl <sub>2</sub> F <sub>3</sub> O <sub>4</sub>	13	0.16
64			<i>n</i> -BuCl	114-115	C <sub>21</sub> H <sub>20</sub> Cl <sub>2</sub> O <sub>5</sub>	2.6	0.8
65			<i>n</i> -BuCl	125-127	C <sub>20</sub> H <sub>17</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.20	7.5
66			<i>n</i> -BuCl	151-152	C <sub>20</sub> H <sub>19</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.076	38
66(+)			<i>n</i> -BuCl/pet. ether	133-135	C <sub>20</sub> H <sub>19</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.05	58
67			<i>n</i> -BuCl	91.5-92	C <sub>20</sub> H <sub>17</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.58	3.4
68			<i>n</i> -BuCl	106-115	C <sub>20</sub> H <sub>19</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.21	8.0
69			<i>n</i> -BuCl	140-142	C <sub>20</sub> H <sub>17</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.51	5.9
70			<i>n</i> -BuCl	98-100	C <sub>20</sub> H <sub>19</sub> Cl <sub>2</sub> FO <sub>4</sub>	0.15	10
71			<i>n</i> -BuCl	138-139	C <sub>20</sub> H <sub>16</sub> Cl <sub>2</sub> F <sub>2</sub> O <sub>4</sub>	0.2	7.5
72			<i>n</i> -BuCl	72-75	C <sub>20</sub> H <sub>13</sub> Cl <sub>2</sub> F <sub>4</sub> O <sub>4</sub> · 0.5 <i>n</i> -C <sub>4</sub> H <sub>9</sub> Cl	0.7	2.3

<sup>a</sup> Analytical results are within ±0.4% of the theoretical value. <sup>b</sup> See footnote b, Table I. <sup>c</sup> See footnote c, Table I.<sup>d</sup> 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

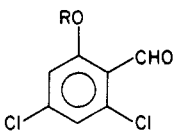
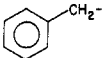
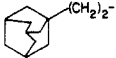

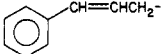
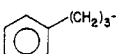
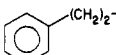
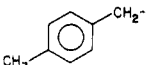
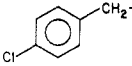
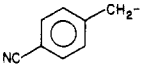
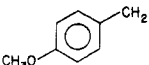
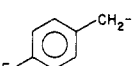
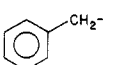
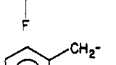
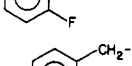
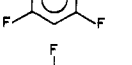
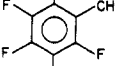



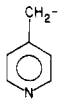



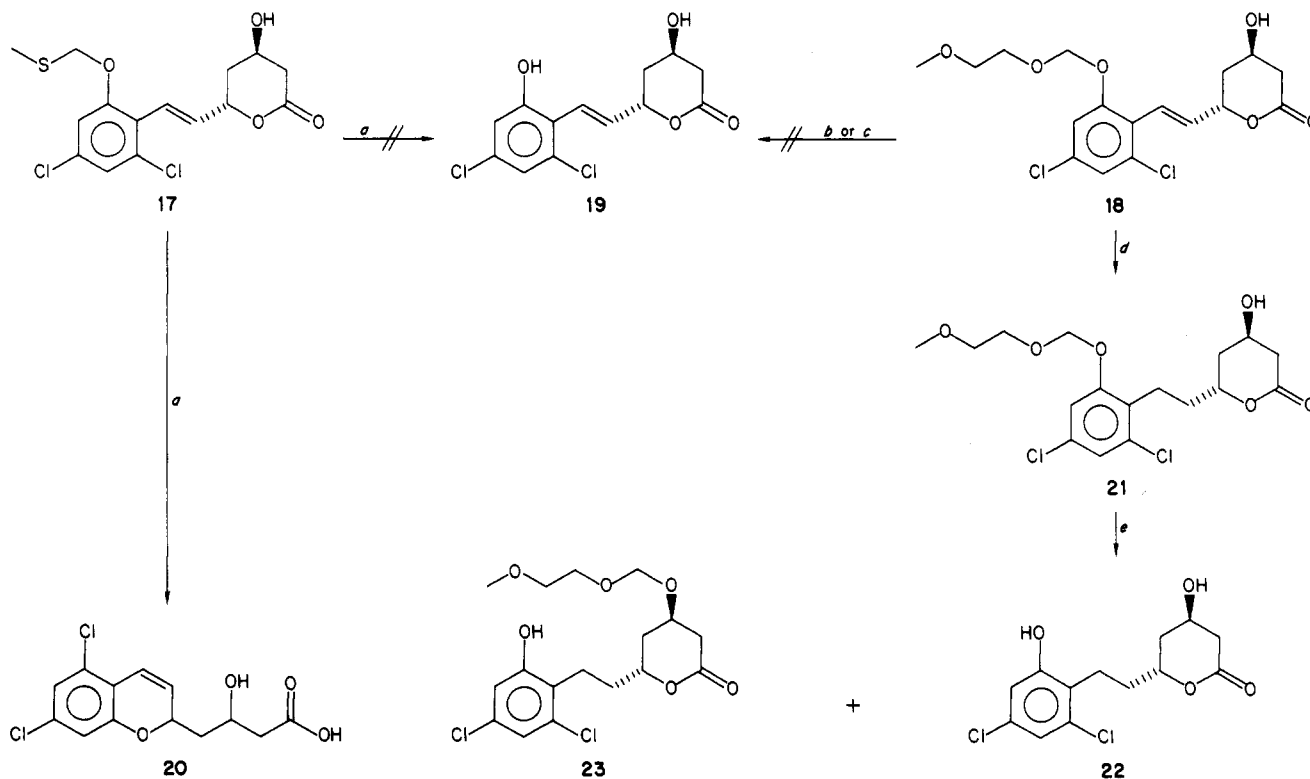
					
no.	R	recryst solvent	mp, °C	formula	anal. <sup>a</sup>
3		hexane	98-100	C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
73	C <sub>2</sub> H <sub>11</sub> -	chromat CH <sub>2</sub> Cl <sub>2</sub> /hexane	oil	C <sub>12</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	<i>b</i>
74 <sup>c</sup>	CH <sub>3</sub> SCH <sub>2</sub> -	EtOH/H <sub>2</sub> O	75-77	C <sub>9</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>2</sub> S	C, H
75	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -		60-63	C <sub>11</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>4</sub>	<i>b, d</i>
76	H <sub>2</sub> C=CHCH <sub>2</sub> -	hexane	97-98	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
77	(CH <sub>3</sub> ) <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )(CH <sub>2</sub> ) <sub>2</sub> -	chromat (Alumina) CH <sub>2</sub> Cl <sub>2</sub> /hexane	oil	C <sub>16</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>2</sub>	<i>b</i>
78		hexane	112-114	C <sub>19</sub> H <sub>22</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
79		hexane	99-101	C <sub>13</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
80		CH <sub>3</sub> CN	109-111	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
81				C <sub>16</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	<i>b, d</i>
82		hexane	96-98	C <sub>15</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>2</sub>	<i>b</i>
83		hexane	93-95	C <sub>15</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
84				C <sub>14</sub> H <sub>9</sub> Cl <sub>3</sub> O <sub>2</sub>	<i>b, d</i>
85		CH <sub>3</sub> CN	179-182	C <sub>15</sub> H <sub>9</sub> Cl <sub>2</sub> NO <sub>2</sub>	C, H, N
86		cyclohexane	95-97	C <sub>15</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>3</sub>	C, H
87		cyclohexane	107-108	C <sub>14</sub> H <sub>9</sub> Cl <sub>2</sub> FO <sub>2</sub>	C, H
88		hexane	108-109.5	C <sub>14</sub> H <sub>9</sub> Cl <sub>2</sub> FO <sub>2</sub>	C, H
89		cyclohexane	101-103	C <sub>14</sub> H <sub>9</sub> Cl <sub>2</sub> FO <sub>2</sub>	C, H
90			127.5-129	C <sub>14</sub> H <sub>8</sub> Cl <sub>2</sub> F <sub>2</sub> O <sub>2</sub>	<i>b, d</i>
91		cyclohexane	120-121.5	C <sub>14</sub> H <sub>5</sub> Cl <sub>2</sub> F <sub>5</sub> O <sub>2</sub>	C, H
92		hexane	97-100	C <sub>20</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	C, H
93		toluene	193-195	C <sub>18</sub> H <sub>12</sub> ClO <sub>2</sub>	C, H, Cl
94		hexane	83-85	C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>2</sub> S	C, H, Cl
95		hexane	65-68	C <sub>12</sub> H <sub>8</sub> Cl <sub>2</sub> O <sub>3</sub>	C, H, Cl

Table III (Continued)

no.	R	recryst solvent	mp, °C	formula	anal. <sup>a</sup>
96			145-148	C <sub>13</sub> H <sub>9</sub> Cl <sub>2</sub> NO <sub>2</sub>	b, d
97				C <sub>13</sub> H <sub>9</sub> Cl <sub>2</sub> NO <sub>2</sub>	b, d
98			120-123	C <sub>13</sub> H <sub>9</sub> Cl <sub>2</sub> NO <sub>2</sub>	b, d
99		n-BuCl	117-118	C <sub>15</sub> H <sub>11</sub> Cl <sub>3</sub> O <sub>3</sub>	b

<sup>a</sup> Analysis for the elements indicated were within  $\pm 0.4\%$  of the theoretical values. <sup>b</sup> <sup>1</sup>H NMR is in full accord with the proposed structure. <sup>c</sup> Reference 11. <sup>d</sup> Used without purification in the next step.

Scheme III



<sup>a</sup>HgCl<sub>2</sub>, H<sub>2</sub>O, CH<sub>3</sub>CN, 80 °C. <sup>b</sup>HF<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. <sup>c</sup>TiCl<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C. <sup>d</sup>H<sub>2</sub>, Rh/C. <sup>e</sup>ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

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

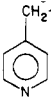
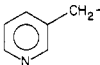
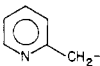
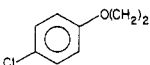
Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solutions were dried over anhydrous MgSO<sub>4</sub> and evaporated under reduced pressure (rotary evaporator). Proton NMR spectra were recorded in CDCl<sub>3</sub>, unless noted otherwise, on either a Varian T-60, EM-390, or NT-360 spectrometer. Chemical shifts are reported in parts per million relative to Me<sub>4</sub>Si as the internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined with a Perkin-Elmer Model 240 elemental analyzer and are within  $\pm 0.4\%$  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 <sup>a</sup>	method <sup>b</sup>
4		cyclohexane	110-112	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> O	A
100	C <sub>5</sub> H <sub>11</sub> -	pet. ether	62-64	C <sub>24</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>2</sub>	A
101 <sup>c</sup>	CH <sub>3</sub> SCH <sub>2</sub> -	EtOH/H <sub>2</sub> O	104-106	C <sub>11</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>2</sub> S	B
102	CH <sub>3</sub> O(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>2</sub> -	chromat CHCl <sub>3</sub> /MeOH	oil	C <sub>13</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>4</sub> <sup>d</sup>	B
103	H <sub>2</sub> C=CHCH <sub>2</sub> -	hexane	89-90	C <sub>12</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>2</sub>	B
104	(CH <sub>3</sub> ) <sub>3</sub> CH <sub>2</sub> CH(CH <sub>3</sub> )(CH <sub>2</sub> ) <sub>2</sub> -	chromat CH <sub>2</sub> Cl/pet. ether	oil	C <sub>18</sub> H <sub>24</sub> Cl <sub>2</sub> O <sub>2</sub>	B
105		hexane	127-127.5	C <sub>21</sub> H <sub>24</sub> Cl <sub>2</sub> O <sub>2</sub>	B
106		hexane	79-80	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> O	B
107		cyclohexane	112-113	C <sub>18</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	C
108		chromat CH <sub>2</sub> Cl <sub>2</sub>		C <sub>18</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>2</sub> <sup>d</sup>	B
109		<i>n</i> -BuCl	136-139	C <sub>17</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub> <sup>d</sup>	A
110		chromat CH <sub>2</sub> Cl <sub>2</sub> /hexane	101-103	C <sub>17</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	B
111		chromat CH <sub>2</sub> Cl <sub>2</sub>	wax	C <sub>16</sub> H <sub>11</sub> Cl <sub>3</sub> O <sub>2</sub> <sup>d</sup>	B
112		chromat CH <sub>2</sub> Cl <sub>2</sub>		C <sub>17</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>2</sub> <sup>d</sup>	C
113		<i>n</i> -BuCl	123-124	C <sub>17</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>3</sub>	C
114		cyclohexane	122-123	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> FO <sub>2</sub>	C
115		<i>n</i> -BuCl	100-101.5	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> FO <sub>2</sub>	C
116		<i>n</i> -BuCl	134-136	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> FO <sub>2</sub>	C
117		chromat CH <sub>2</sub> Cl <sub>2</sub>	125-130	C <sub>16</sub> H <sub>10</sub> Cl <sub>2</sub> F <sub>2</sub> O <sub>2</sub> <sup>d</sup>	C
118		cyclohexane	108.5-113	C <sub>16</sub> H <sub>7</sub> Cl <sub>2</sub> F <sub>3</sub> O <sub>2</sub> <sup>d</sup>	C
119		chromat CH <sub>2</sub> Cl <sub>2</sub>	oil	C <sub>22</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>2</sub> <sup>d</sup>	B
120		<i>n</i> -BuCl	174-177	C <sub>20</sub> H <sub>14</sub> Cl <sub>2</sub> O <sub>2</sub>	B
121		<i>n</i> -BuCl/hexane	113-115	C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>2</sub> S	B
122		<i>n</i> -BuCl/hexane	96-99	C <sub>14</sub> H <sub>10</sub> Cl <sub>2</sub> O <sub>3</sub>	B

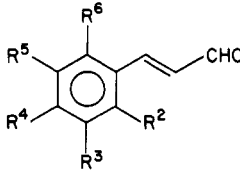








Table IV (Continued)

no.	R	recryst solvent	mp, °C	formula <sup>a</sup>	method <sup>b</sup>
123				C <sub>11</sub> H <sub>11</sub> Cl <sub>2</sub> O <sub>2</sub> <sup>d</sup>	C
124				C <sub>11</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>2</sub> <sup>d</sup>	C
125				C <sub>11</sub> H <sub>11</sub> Cl <sub>2</sub> NO <sub>2</sub> <sup>d</sup>	C
126		CH <sub>3</sub> CN	109-111	C <sub>17</sub> H <sub>13</sub> Cl <sub>3</sub> O <sub>3</sub> <sup>d</sup>	A

<sup>a</sup> Analytical results are within  $\pm 0.4\%$  of the theoretical values. <sup>b</sup> Methods: (A)<sup>4</sup> CH<sub>3</sub>CHO, (B)<sup>5</sup> C<sub>6</sub>H<sub>11</sub>N=CHCH<sub>2</sub>Li, (C)<sup>6</sup> LiCH=CHOEt. <sup>c</sup> See footnote c, Table III. <sup>d</sup> No analysis; <sup>1</sup>H NMR are in full accord with the proposed structure.

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



no.	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	recryst solvent	mp, °C	formula <sup>a</sup>	method <sup>b</sup>
127	Cl	H	H	H	Cl	bp 126-31 (1 mm)	50-55	C <sub>9</sub> H <sub>6</sub> Cl <sub>2</sub> O	A
128		H	H	H	H	hexane	73-75	C <sub>13</sub> H <sub>12</sub> O	c
129	CH <sub>3</sub>	H	CH <sub>3</sub>	H	H	chromat CH <sub>2</sub> Cl <sub>2</sub>	oil	C <sub>11</sub> H <sub>12</sub> O <sup>d</sup>	A
130	Cl	H		H	Cl	cyclohexane	75-77	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> O <sub>2</sub>	B
131	CH <sub>3</sub>	H		H	CH <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> /hexane	65.5-67	C <sub>18</sub> H <sub>16</sub> O <sub>2</sub>	C
132	Cl	Cl		H	H	chromat CH <sub>2</sub> Cl <sub>2</sub>	142-146	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> FO <sub>2</sub> <sup>d</sup>	C
133	Cl	H		H	Cl	CH <sub>3</sub> CN	112-114	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> FO <sub>2</sub> <sup>d</sup>	C
134	H	Cl		Cl	C <sub>5</sub> H <sub>11</sub> O-	chromat CH <sub>2</sub> Cl <sub>2</sub> /hexane	oil	C <sub>14</sub> H <sub>16</sub> Cl <sub>2</sub> O <sub>2</sub>	A

<sup>a</sup> Analytical results are within  $\pm 0.4\%$  of the theoretical unless otherwise noted. <sup>b</sup> See footnote b, Table IV. <sup>c</sup> Prepared by the method of H. Newman: *J. Org. Chem.* 1973, 38, 2254. <sup>d</sup> No analysis; <sup>1</sup>H 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-dichlorosalicylaldehyde (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<sub>2</sub>O (1 L). Collection of the solid gave 3 (15.9 g, 100%) which was recrystallized; NMR  $\delta$  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.<sup>6</sup> 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<sup>7</sup> (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<sub>3</sub> (25 mL), diluted with H<sub>2</sub>O (100 mL), and extracted with Et<sub>2</sub>O (2  $\times$  200 mL). The organic extracts were combined, washed with brine (2  $\times$  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<sub>2</sub>Cl<sub>2</sub> (200 mL) provided a forerun containing tetrabutyltin which was discarded. Continued elution with CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH (98:2, v/v; 1500 mL) provided 4 as a pale yellow solid which was recrystallized (6.4 g, 70%); NMR  $\delta$  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.<sup>8</sup> 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<sub>2</sub>O (100 mL) and extracted with Et<sub>2</sub>O (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  $\delta$  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<sub>2</sub>O (500 mL), and extracted with Et<sub>2</sub>O (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  $\delta$  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-2H-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<sub>2</sub>O (400 mL), and extracted with Et<sub>2</sub>O (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  $\delta$  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<sub>2</sub>Cl<sub>2</sub>/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<sub>2</sub>Cl<sub>2</sub>/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  $\delta$  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  $\delta$  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<sub>20</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>4</sub>) 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-2H-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<sub>2</sub>Cl<sub>2</sub> (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  $\delta$  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-2H-pyran-2-one (8a(±)).** A solution of 8a(±) (1.75 g, 4.44 mmol) in *l*-(-)- $\alpha$ -methylbenzylamine (10 mL) was stirred for 18 h at ambient temperature and then poured into H<sub>2</sub>O (50 mL). The aqueous mixture was acidified with 6 N HCl and the resulting solid was collected and suspended in Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (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  $\delta$  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<sub>28</sub>H<sub>31</sub>Cl<sub>2</sub>NO<sub>4</sub>) C, H, N.

The Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>Cl<sub>2</sub> (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 amorphous solid, mp 130–132 °C; NMR  $\delta$  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<sub>28</sub>H<sub>31</sub>Cl<sub>2</sub>NO<sub>4</sub>) C, H, N.

**(+)-trans-(E)-6-[2-[2,4-Dichloro-6-(phenylmethoxy)phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-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<sub>2</sub>O and acidified with 6 N HCl. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>Cl<sub>2</sub> (1:4, v/v) gave the lactone 8a(+) as a solid which was recrystallized to provide colorless clusters (0.33 g);  $[\alpha]_D^{25} +16.6^\circ$  (c 1.0, CHCl<sub>3</sub>); NMR  $\delta$  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-2H-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);  $[\alpha]_D^{25} -17.7^\circ$  (c 1.0, CHCl<sub>3</sub>); NMR  $\delta$  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)<sub>3</sub> in CDCl<sub>3</sub>; 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)dimethylsilyloxy]naphthalene (10).** A solution of 9<sup>b</sup> (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  $-78^{\circ}\text{C}$  under an atmosphere of  $\text{N}_2$ . After an additional 3 min at  $-78^{\circ}\text{C}$ , *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  $\text{Et}_2\text{O}$  (300 mL) and  $\text{H}_2\text{O}$  (300 mL). The  $\text{Et}_2\text{O}$  layer was separated and washed with  $\text{H}_2\text{O}$  ( $2 \times 200$  mL), dried, filtered, and evaporated to yield **10** (22.4 g, 90%) as a light yellow oil; NMR  $\delta$  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  $\text{CH}_2\text{Cl}_2$  (250 mL) and  $\text{CH}_3\text{OH}$  (250 mL) at  $-78^{\circ}\text{C}$  until the color of the solution turned blue (ca. 30 min). After the excess ozone was purged by bubbling  $\text{N}_2$  through the solution,  $\text{NaBH}_4$  (2.85 g, 75 mmol) was added and the reaction mixture was stirred at  $20^{\circ}\text{C}$  for 2 h. The reaction mixture was then evaporated at  $<30^{\circ}\text{C}$ , diluted with 0.1 N HCl (750 mL), and stirred vigorously at  $20^{\circ}\text{C}$  before filtration. Trituration of the sticky solid with hexane and subsequent crystallization from  $\text{HOAc-H}_2\text{O}$  provided **11** (10.9 g, 64%), mp  $161\text{--}163^{\circ}\text{C}$ , as colorless needles. Recrystallization from  $\text{HOAc-H}_2\text{O}$  afforded an analytical sample, mp  $166\text{--}167^{\circ}\text{C}$ ; NMR ( $\text{Me}_2\text{SO}$ )  $\delta$  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. ( $\text{C}_{10}\text{H}_{10}\text{Cl}_2\text{O}_3$ ) 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  $\text{NaHCO}_3$  (3.7 g, 44 mmol) was stirred at  $55\text{--}60^{\circ}\text{C}$  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  $\text{Et}_2\text{O}$  (300 mL) and  $\text{H}_2\text{O}$  (800 mL). The  $\text{Et}_2\text{O}$  layer was washed with  $\text{H}_2\text{O}$  ( $2 \times 200$  mL), dried, filtered, and evaporated to afford **12** (8.8 g, 87%) as a brown oil; NMR  $\delta$  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  $\delta$  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  $50\text{--}60^{\circ}\text{C}$  for 0.5 h. The reaction mixture was cooled, diluted with  $\text{H}_2\text{O}$  (200 mL), and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 100$  mL). The  $\text{Et}_2\text{O}$  extracts were combined and washed with  $\text{H}_2\text{O}$  ( $3 \times 200$  mL), dried, filtered, and evaporated. The residual brown oil was chromatographed on silica gel using  $\text{CH}_2\text{Cl}_2$ /hexane (1:1, v/v) as eluant to give **14** (2 g, 54%); NMR  $\delta$  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  $\text{Et}_2\text{O}$  (25 mL) was added dropwise to a stirred suspension of LAH (139 mg, 3.65 mmol) in  $\text{Et}_2\text{O}$  (10 mL) under a  $\text{N}_2$  atmosphere. After stirring for 15 min, the reaction mixture was cooled to  $0^{\circ}\text{C}$  and worked up by the sequential addition of  $\text{H}_2\text{O}$  (0.14 mL), 20% NaOH (0.11 mL), and  $\text{H}_2\text{O}$  (0.41 mL). After the mixture was stirred for 0.5 h at  $20^{\circ}\text{C}$ , anhydrous  $\text{MgSO}_4$  was added and the mixture was filtered and evaporated to yield **15** (1.6 g, 87%), mp  $95\text{--}96^{\circ}\text{C}$ , as a white powder. Recrystallization from *n*-BuCl–hexane gave an analytical sample, mp  $95.5\text{--}96.5^{\circ}\text{C}$ ; NMR  $\delta$  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  $\text{CH}_2\text{Cl}_2$  (10 mL) was added rapidly to a suspension of pyridinium chlorochromate (1.46 g, 6.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) at  $20^{\circ}\text{C}$ . After stirring for 2 h, the reaction mixture was diluted with  $\text{Et}_2\text{O}$  (30 mL) and filtered through silica gel (40 g). The black residue in

the reaction vessel was washed with  $\text{Et}_2\text{O}$  ( $3 \times 50$  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  $\delta$  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-2H-benzopyran-2-yl)-2-hydroxybutyric Acid (20)**. The MTM ether **17** was cleaved by the general method of Holton.<sup>10</sup>  $\text{HgCl}_2$  (1.5 g, 5.5 mol) was added to a solution of the MTM ether **17** (1.3 g, 4.3 mmol) in  $\text{CH}_3\text{CN}$  (20 mL) containing  $\text{H}_2\text{O}$  (5 mL). After refluxing for 9 h, the mixture was cooled to ambient temperature and diluted with  $\text{Et}_2\text{O}$  (100 mL). The ether layer was separated, washed with  $\text{H}_2\text{O}$  ( $3 \times 100$  mL), dried, and evaporated to give a viscous oil (0.9 g). The oil was flash chromatographed on a  $5 \times 15$  cm column of silica gel (230–400 mesh). Elution with acetic acid/ $\text{CH}_2\text{Cl}_2$  (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  $\delta$  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. ( $\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{O}_4$ ) 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-2H-pyran-2-one (21)** was prepared from **18** (800 mg, 2 mmol) by the procedure used to synthesize **8a**( $\pm$ ) and purified by chromatography to provide a colorless oil (500 mg); NMR  $\delta$  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-2H-pyran-2-one (22)**. The MEM ether group of **21** was removed by the general procedure of Corey.<sup>12</sup>  $\text{ZnBr}_2$  (2 g, 8.9 mmol) was added to a magnetically stirred solution of MEM ether (650 mg, 1.7 mmol) **21** in  $\text{CH}_2\text{Cl}_2$  (8 mL). After 1.5 h another 2 g of  $\text{ZnBr}_2$  was added and stirring was continued for another 0.5 h. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  solution (50 mL), diluted with  $\text{Et}_2\text{O}$  (150 mL), and acidified with 12 N HCl. The organic layer was separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  ( $2 \times 50$  mL). The organic extracts were combined, washed with  $\text{H}_2\text{O}$  ( $2 \times 50$  mL), dried, and evaporated to give a yellow gum. The gum was flash chromatographed on a  $5 \times 15$  cm column of silica gel (230–400 mesh). Elution with acetone/ $\text{CH}_2\text{Cl}_2$  (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  $\delta$  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  $3 \times 15$  cm column of silica gel (230–400 mesh). Elution with acetone/ $\text{CH}_2\text{Cl}_2$  (1:6, v/v; 140 mL) provided **23** as a gum (70 mg); NMR  $\delta$  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 ( $\text{M}^+$ ).

**trans-6-[2-[2,4-Dichloro-6-[(4-(trifluoromethyl)phenyl)methoxy]phenyl]ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-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  $\delta$  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);  $^{19}\text{F}$  NMR ( $\text{CFCl}_3$ )  $\delta$   $-6.20$  (s).

**Isolation of HMG-CoA Reductase.** Carried out as previously described.<sup>3</sup>

**Acknowledgment.** We are indebted to Drs. R. F. Hirschmann, E. H. Cordes, and P. S. Anderson for their encouragement throughout the course of this investigation, to Dr. W. C. Randall and staff for analytical support, to Drs. B. H. Arison and D. W. Cochran for NMR spectra, and to M. Z. Banker for manuscript preparation.

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