3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 1. Structural Modification of 5-Substituted 3,5-Dihydroxypentanoic Acids and Their Lactone Derivatives

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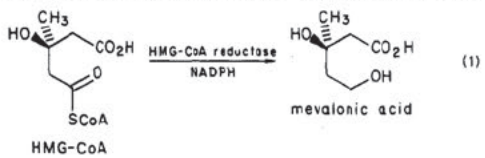
A series of 5-substituted 3,5-dihydroxypentanoic acids and their derivatives have been prepared and tested for inhibition of HMG-CoA reductase in vitro. In general, unless a carboxylate anion can be formed and the hydroxy groups remain unsubstituted in an erythro relationship, inhibitory activity is greatly reduced. Furthermore, only one enantiomer of the ring-opened form of lactone **6a(±)** possesses the activity displayed by the racemate. Insertion of a bridging unit other than ethyl or (*E*)-ethenyl between the 5-carbinol moiety and an appropriate lipophilic moiety (e.g., 2,4-dichlorophenyl) attenuates activity.

Formation of the atheromatous plaque or atheroma is accompanied by the localized deposition of plasma lipids, primarily cholesteryl esters, in the intima of the arterial wall.[1,2] Growth of the atheroma eventually leads to constriction of the coronary arterial lumen and ultimately results in atherosclerosis and coronary heart disease (CHD), the major cause of death and disability in Western countries. These observations, coupled with the compelling epidemiological evidence implicating hypercholesterolemia as a primary risk factor for CHD,[3,4] have stimulated research on the development of therapeutic agents for preventing and treating atherosclerosis based on the attenuation of plasma cholesterol levels.[5] The results of the recently completed Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)[6] provide strong support for the basis of this approach. The LRC-CPPT clearly demonstrated that reduction of low-density lipoprotein cholesterol (LDL-C) through dietary modification and treatment with the bile acid sequesterant cholestyramine, either alone or in combination, diminished the incidence of CHD morbidity and mortality in hypercholesterolemic men at high risk for CHD. Nevertheless, the reduction of dietary cholesterol and saturated fat intake and the use of bile acid sequesterants often fail to lower elevated plasma LDL-C levels to the desired extent, particularly in patients with familial hypercholesterolemia (FH).[7]

An attractive and potentially more efficacious way to lower plasma cholesterol levels would be to control de novo cholesterogenesis by selectively inhibiting an early biosynthetic step. The highly functionalized fungal metabolites compactin (ML-236B, CS-500)[8] and mevinolin (MK-803)[9] are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase [HMG-CoA reductase; mevalonate:NADP$^+$ oxidoreductase (CoA acylating), EC 1.1.1.34],[10] which catalyzes the conversion of HMG-CoA to mevalonic acid (eq 1). Indeed, mevinolinic acid (**1**), the dihydroxy acid form of mevinolin, is the most potent HMG-CoA reductase inhibitor (K_i = 0.6 nM) reported to date.[9] Of even greater interest are the findings that compactin[11,12] and mevinolin[9,13] are highly effective hypocholesterolemic agents in several animal species and man. Subsequent to the first reports disclosing the structure[14] and biological activity[8] of compactin, a series of studies directed toward the development of structurally simplified HMG-CoA reductase inhibitors were initiated in these Laboratories. Described in this paper are the results of our initial study,[15] which served to delineate key



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(1) Ross, R. *Annu. Rev. Med.* **1979**, *30*, 1.
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(12) (a) Yamamoto, A.; Sudo, H.; Endo, A. *Atherosclerosis (Shannon, Irel.)* **1980**, *35*, 259. (b) Mabuchi, H.; Haba, T.; Tatami, R.; Miyamoto, S.; Sakai, Y.; Wakasugi, T.; Watanabe, A.; Koizumi, J.; Takeda, R. *N. Engl. J. Med.* **1981**, *305*, 478.
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(14) The X-ray crystal structure of compactin was first reported by Brown, A. G.; Smale, T. C.; King, T. J.; Hansenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165. Note that the relative configuration in Figure 1 of the cited reference does not agree with the crystal coordinates; we present here the correct relative and absolute stereochemical configuration of compactin.

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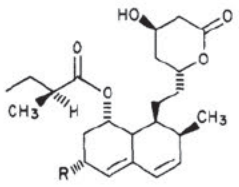
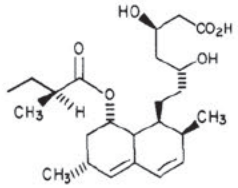
SARs for compactin-like mimics and afforded a series of moderately effective HMG-CoA reductase inhibitors typified by the ring-opened form of lactone **6a(+)**.



compactin, R = H
mevinolin, R = CH_3



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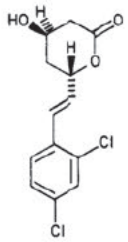


6a(+)

Chemistry. The compounds prepared for this study are listed in Tables I–III. Their syntheses from the corresponding aldehydes, exemplified by **2**, are shown in Schemes I–III. Condensation of aldehyde **2** with the dianion of ethyl acetoacetate[16] followed by borohydride reduction, basic hydrolysis, acidification, and azeotropic removal of water provided a mixture of the trans (**6a(±)**) and cis (**6b(±)**) lactones which subsequently was separated by chromatography (Scheme I). The use of MeOH in the borohydride reduction step was found to be advantageous; replacement of MeOH by EtOH produced some of the corresponding ethyl ester which was more resistant to hydrolysis. The resolution of **6a(±)** was accomplished via formation and chromatographic separation of the diastereomeric (*R*)-α-methylbenzylamines followed by basic hydrolysis and relactonization to yield **6a(+)** and **6a(−)**.

Hydrolysis and acidification of 5-hydroxy-3-keto ester **3** without prior reduction resulted in spontaneous lactonization to enol lactone **4**. Numerous attempts to reduce **4** to hydroxy lactone **6**, either catalytically or via metal hydrides, were unsuccessful. Treatment of lactone **6a(±)** with NH_3 provided the erythro amide **10**. Catalytic reduction of lactone **6a(±)** provided compound **7** containing a saturated bridging unit. The lactol ethers **8** and **9** were prepared by diisobutylaluminum hydride (Dibal) reduction of **6a(±)** followed by treatment with MeOH in the presence of pyridinium *p*-toluenesulfonate (PPTS).

The syntheses of methyl lactones **13**, **16**, and **17** are illustrated in Scheme II. A tin-mediated aldol condensation of aldehyde **2** with 2-acetoxypropene following a slightly modified procedure of Noltes et al.[17] provided 4-hydroxy ketone **11** in high yield. Acylation of **11** with 2-bromoacetyl bromide in the presence of pyridine furnished bromo acetate **12** which was ring closed to 4-hydroxy-4-methyl lactone **13** via an intramolecular Reformatsky reaction.[18] Substitution of triethylamine for pyridine in the acylation step resulted in elimination of the 2-bromoacetoxy moiety and isolation of the resultant dienone.

An alternate route to lactone **13** starting from 4-hydroxy ketone **11** was investigated. This route involved sequential acylation, intermolecular Reformatsky reaction with ethyl 2-bromoacetate, basic hydrolysis, acidification, and lactonization. This route was abandoned in favor of the more efficient two-step route (vide supra). Ethylene lactone **13a** was reduced in the same manner as **6a(±)** to provide the corresponding ethyl-bridged compound **16**. Refluxing a solution of **13a** and toluene in the presence of PTSA (trace) resulted in the smooth conversion of **13a** to **17**.

5-Methoxy-3-hydroxyheptenoic acid **20** was prepared by treating the dimethyl acetal of **2** with diketene (1 equiv) in the presence of $TiCl_4$ by using the general procedure of Izawa and Mukaiyama[19] followed by borohydride reduction, basic hydrolysis, and acidification of the resultant 3-keto ester **19** as shown in Scheme III. A similar condensation of aldehyde **2** provided a mixture of 3-keto ester **3** and dihydro lactone **4** and, thus, was a less expeditious route to target lactone **6** than was the dianion procedure (Scheme I).

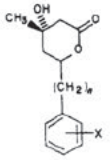
The previously undescribed requisite aldehydes were prepared as shown in Schemes IV–VIII. The synthesis of the α,β-unsaturated aldehyde **55a** needed for elaborating lactone **55** is shown in Scheme IV with phenanthrene-4-carboxaldehyde as starting material. This procedure was also used to prepare the known α,β-unsaturated aldehyde precursors for lactones **56–58**.

The 3-(decahydronaphthyl)propanals **25** and **27** (precursors to **51** and **52**) were elaborated from **21** as shown in Scheme V. After high-pressure hydrogenation of **22**, the acid **23** was converted to aldehyde **25** by the Burgstahler modification of the Rosenmund reduction.[20] The ethyl ester of **23** (**24**, isolated in about an equal amount during the workup of **23**) was isomerized with $AlCl_3$ (2 equiv) at room temperature and subsequently hydrolyzed to acid **26**, which was converted to aldehyde **27** in the same manner used for **23** → **25**.

The Dibal reduction of nitriles **29**, **32**, and **34** (Scheme VI) provided the aldehydes requisite for preparing lactones **47**, **48**, and **53**, respectively. Aldehyde **37** (precursor to **44**)[21] was prepared by alkylation of phenol **36** with the diethyl acetal of 2-bromoacetaldehyde followed by hydrolysis (Scheme VII).

Finally, conversion of cinnamaldehyde **2** to propargylaldehyde **41** (precursor to **42**) was effected via the four step sequence **2** → **38** → **39** → **40** → **41** by using the general method of Allen and Edens[22] as shown in Scheme VIII.

(15) During the course of this study, a series of mevalonolactone derivatives of the general structure were reported to inhibit



HMG-CoA reductase by Sato et al.: Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneko, I., Shimada, Y. *Chem. Pharm. Bull.* **1980**, *28*, 1509.

(16) Huckin, S. N.; Weiler, L. *Tetrahedron Lett.* **1971**, 4835.

(17) Noltes, J. G.; Verbeek, F.; Creemers, H. M. J. C. *Organometal. Chem. Synth.* **1970–1971**, *1*, 57. In the present case, (tributylstannyl)acetone was prepared in situ.

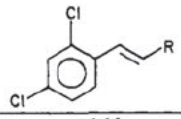
(18) For a general method, see: Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705.

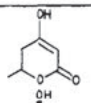
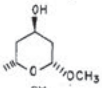
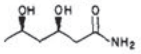
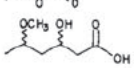
(19) Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 161.

(20) Burgstahler, A. W.; Weigel, L. O.; Shaefer, C. G. *Synthesis* **1976**, 767.

(21) During the course of this investigation, the 4*R*,6*R* dechloro analogue was prepared from tri-*O*-acetyl-D-glucal as a possible HMG-CoA reductase inhibitor by Yang et al.: Yang, Y. L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305.

Table I. Effects of Lactone Modification and Stereochemistry



no.	R	recryst solvent	yield, %	mp, °C	formula[a]	concn, μg/mL	% inhib[b]
4[c,d]		EtOAc	52	168–169	$C_{13}H_{12}Cl_2O_3$	2	0
						10	12
						50	15
6a(±)[e]		acetone/hexane	33	148–150	$C_{13}H_{12}Cl_2O_3$	1	13
						5	41
						10	64
						20	84
6b(±)		acetone/hexane	17	115–117	$C_{13}H_{12}Cl_2O_3$	2	4
						5	6
						10	27
						20	17
						50	18
6a(+)		*n*-BuCl	25	114–116	$C_{13}H_{12}Cl_2O_3$	1	26
						2	45
						5	66
						10	72
						20	86
6a(−)		*n*-BuCl	44	114–116	$C_{13}C_{12}Cl_2O_3$	1	0
						2	0
						4	0
						8	0
8[c]		chromat. acetone/CH_2Cl_2	33	wax	$C_{14}H_{16}Cl_2O_3 \cdot {}^1/_4H_2O$	2	0
						4	2
						6	4
9[c]		chromat. acetone/CH_2Cl_2	64	88–93	$C_{14}H_{16}Cl_2O_3$	2	0
						4	0
						8	6
						10	0
10[c]		acetone/hexane	63	117–118	$C_{13}H_{15}Cl_2NO_3$	1	0
						2	0
						4	0
						8	0
13a		*n*-BuCl	35[f]	136–138	$C_{14}H_{14}Cl_2O_3$	1	11
						2	21
						4	36
						10	61
13b		*n*-BuCl/hexane	5.4	135–137	$C_{14}H_{14}Cl_2O_3$	2	3
						4	7
						10	5
						25	15
17		chromat. $CHCl_3$/MeOH	90	108–110	$C_{14}H_{12}Cl_2O_2$	2	0
						4	3
						10	3
						25	5
20[g]		chromat. CH_2Cl_2/HOAc	42[h]	gum	$C_{14}H_{16}Cl_2O_4$[i]	1	0
						2	0
						5	0
						10	0

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] See Experimental Section for protocol. [c] Tested in the form indicated since carboxylate anion could not be formed under this testing protocol. [d] pK_a = 5.22 (30% EtOH). [e] When tested in the lactone form only 25% inhibition was observed at 50 μg/mL. [f] Yield from **12**. [g] About a 4:3 ratio of erythro and threo. [h] Overall yield from **18**. [i] Anal. Calcd: C, 52.68. Found: C, 52.02.

The synthesis of **43** (the *Z* isomer of **6a(±)**) was accomplished by the catalytic hydrogenation (Lindlar) of **42**.

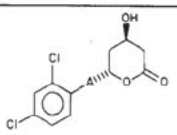
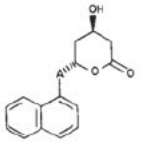
Biological Results and Discussion

The compounds listed in Tables I–IV were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase. During the initial phase of this study, both the lactone and the ring-opened sodium dihydroxycarboxylate forms of each compound were tested for intrinsic inhibitory activity. In each instance, the sodium dihydroxycarboxylate form proved more active than the lactone form (see Table I, footnote *e*). Accordingly, subsequent tests were done exclusively on the sodium dihydroxycarboxylate forms unless noted otherwise.

The contributions of lactone moiety stereochemistry and functionality to intrinsic inhibitory activity in compound **6** are illustrated in Table I. Separation of the lactone mixture **6** into the racemic cis (**6b(±)**) and trans (**6a(±)**) isomers showed that activity resided principally in the

(22) Allen, C. F. H.; Edens, C. O., Jr. "Organic Syntheses"; Wiley, New York, 1955; Collect. Vol. III.

Table II. Effects of Bridge Modification

no.	A	recryst solvent	yield, %	mp, °C	formula[a]	concn, μg/mL	% inhib[b]
							
7		*n*-BuCl	60	96–98	$C_{13}H_{14}Cl_2O_3$	1	29
						2	38
						5	57
						10	80
16[c]		chromat. CH_2Cl_2/acetone	50	87–88	$C_{14}H_{16}Cl_2O_3$	1	14
						2	26
						4	37
						8	63
42		chromat. CH_2Cl_2/acetone	11[d]	viscous oil	$C_{13}H_{10}Cl_2O_3$	0.625	0
						3.125	8
43		chromat.[e] IPA/hexane	50	95–98	$C_{13}H_{12}Cl_2O_3$	0.625	0
						3.125	0
44		chromat. CH_2Cl_2/acetone	4.2[d]	oil	$C_{12}H_{12}Cl_2O_4$	1	21
						2	24
						4	18
						10	21
45		*n*-BuCl	13[d]	133–136	$C_{11}H_{10}Cl_2O_3$	5	4
						10	26
						20	27
						50	23
							
46		CH_2Cl_2/*n*-C_4H_9Cl	24[d]	104–107	$C_{15}H_{14}O_3$	5	16
						10	9
						20	7
						50	18
47		chromat. CH_2Cl_2/acetone	9.5[d]	gum	$C_{17}H_{18}O_3 \cdot {}^1/_2H_2O$	5	19
						10	29
						20	45
						50	61
48		chromat. CH_2Cl_2/acetone	16[d]	oil	$C_{18}H_{20}O_3 \cdot {}^1/_{20}C_3H_6O$	2	11
						5	7
						10	25
						25	35

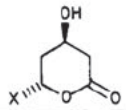
[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] See Experimental Section for protocol. [c] Equatorial 4-Me in lactone by reduction of **13a**. [d] Overall yield from aldehyde. [e] HPLC purification on Dupont silica 10/30 with *i*-PrOH–hexane (1:19, v/v) at 2 mL/min. Times of elution are 13.2 min for **42** and 21.8 min for **43**.

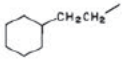
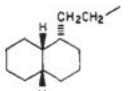
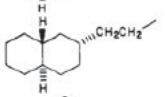
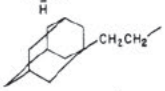
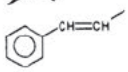
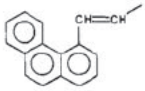
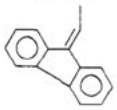
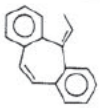
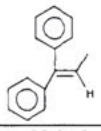
racemic trans lactone (**6a(±)**). Resolution of **6a(±)** afforded enantiomers **6a(+)** and **6a(−)**; their evaluation showed that the activity displayed by the racemate resulted solely from the dextrorotatory isomer. The addition of a methyl group to the 4-position of **6a(±)** to give trans lactone **13a**, a compound which more closely resembles the HMG moiety of the substrate HMG-CoA, did not alter activity appreciably. However, cis lactone **13b**, which possesses the opposite relative stereochemistry at C-4, was much less active as anticipated from the results obtained for **6a(±)** and **6b(±)**. Interestingly, oxidation of the 4-hydroxyl group of **6a(±)** to provide enol **4** greatly reduced activity. This result is a likely consequence of the fact that **4** readily forms the sodium salt of the enolate and, therefore, fails to undergo ring opening to afford the required carboxylate anion under alkaline conditions. Replacement of the enolic hydroxyl group in **4** with a methyl group to provide **17** further reduced activity. Replacement of the carboxyl group in the ring-opened form of **6a(±)** with a carboxamido group (**10**) ablated activity as did conversion of the 5-hydroxl group to the corresponding methyl ether (**20**). These results demonstrate the important contributions of the carboxylate and 5-hydroxyl groups to activity. Finally, it should be noted that lactol ethers **8** and **9** displayed greatly diminished activities.

The effects of altering the moiety bridging the aromatic and the lactone fragments in **6a(±)** on intrinsic inhibitory activity are shown in Table II. Saturation of the ethenyl bridge in **6a(±)** and its 4-methyl derivative **13a(±)** gave ethyl-bridged compounds **7** and **16**, respectively, with little change in activity. However, other modifications of the bridge such as replacement with the ethynyl (**42**), *cis*-ethenyl (**43**), and oxymethylene (**44**) groups resulted in loss of activity as did complete removal (**45**) of the bridging moiety. In a companion series of naphthalene analogues (Table II), compound **47** containing the saturated two-carbon bridge proved superior. Increasing the length of the bridge to three carbons (**48**) reduced activity and elimination of the bridge to provide **46** further reduced activity.

The results of various carbocyclic moieties substituted at the 6-position of the lactone ring are shown in Table

Table III. Effects of 6-Substitution



no.	X	recryst solvent	yield,[a] %	mp, °C	formula[b]	concn, μg/mL	% inhib[c]
49		Et_2O/pet. ether	~8–10	56–58	$C_{11}H_{18}O_3$	5 10 20 50	1 0 6 36
50[d,e]		Et_2O/hexane	~8–10	69–70.5	$C_{13}H_{22}O_3$[f]	5 10 20 50	23 6 17 34
51[e,g]		Et_2O/hexane	~8–10	68–71	$C_{17}H_{28}O_3 \cdot 0.1H_2O$[h]	5 10 20 50	15 22 44 70
52[e,i]		Et_2O/hexane	~8–10	102–110	$C_{17}H_{28}O_3$	1 5 12.5	1 13 28
53[e,j]		Et_2O/hexane	~8–10	122–129	$C_{17}H_{26}O_3$	1 5 12.5	18 16 28
54		Et_2O	23	96–98	$C_{13}H_{14}O_3$	5 10 20 50	3 15 14 31
55		*n*-BuCl	25	140–142	$C_{21}H_{18}O_3$	0.35 0.75 1.0	39 58 64
56[k]		*n*-BuCl	3	151–152	$C_{19}H_{16}O_3$	0.1 0.2 0.4 0.8	25 48 61 81
57[l]		*n*-BuCl	12	gum	$C_{21}H_{18}O_3$	0.1 0.2 0.4	20 34 42
58[m]		*n*-BuCl	10	143–144	$C_{19}H_{18}O_3$	0.1 0.2 0.4 0.8	22 36 14 20

[a] Overall yield from aldehyde. [b] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [c] See Experimental Section for protocol. [d] Mixture of trans/cis; 1.4/1. [e] Percent inhibition calculated as if contribution of cis isomer was zero. [f] Anal. Calcd: C, 68.99. Found: C, 68.54. [g] Mixture of trans/cis; 28/1. [h] Anal. Calcd: C, 72.82. Found: C, 72.27. [i] Mixture of trans/cis; 3.8/1. [j] Mixture of trans/cis; 2/1. [k] Preparation of aldehyde, mp 112–116 °C; Hennion, G. F.; Fleck, B. R. *J. Am. Chem. Soc.* **1955**, *77*, 3253. [l] Preparation of aldehyde, mp 96–98 °C; Bergmann, E. D.; Weiler-Feilchenfeld, H.; Mandel, N. *Vietnamica Chim. Acta* **1966**, 129; *Chem. Abstr.* **1972**, *72*, 3276s. [m] Preparation of aldehyde, mp 42–44 °C; Kohler, E. P.; Larsen, R. G. *J. Am. Chem. Soc.* **1935**, *57*, 1452.

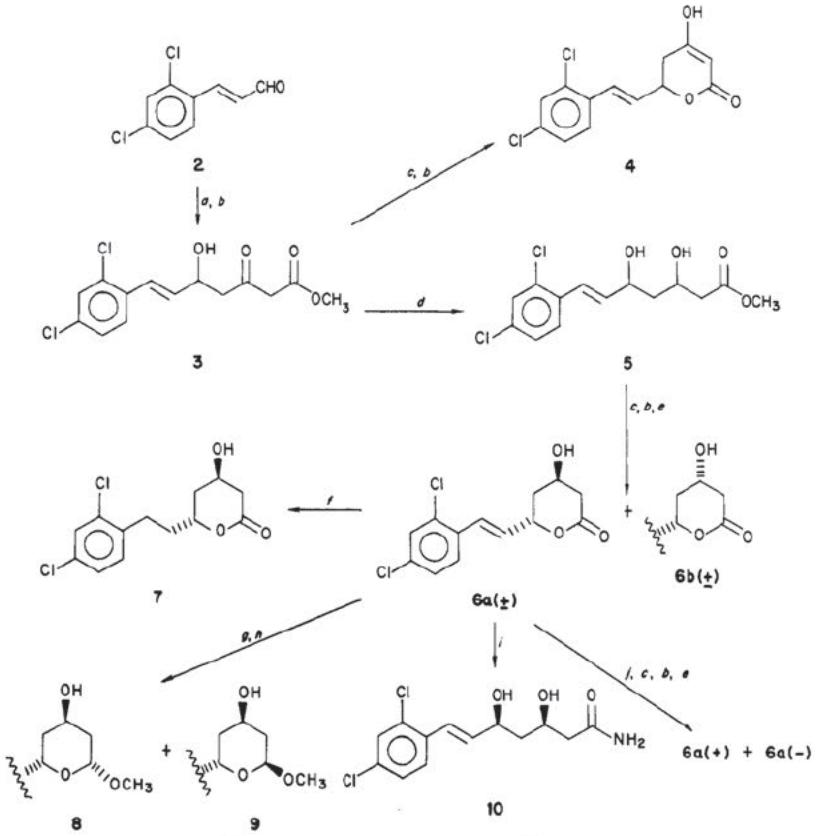
III. The decahydronaphthalenes **51** and **52** and the adamantyl compound **53** all possessed similar activity, while the cyclohexanes **49** and **50** were less active. Aromatization of the cyclohexane ring to give the phenyl derivative **54** had little effect on activity. However, substitution of the bridging moiety with larger aromatic groups such as those in compounds **55–57** increased activity about 10-fold, i.e., to about 1% of the inhibitory activity of compactin. Scission of the 4a–4b bond of compound **56** provided a less compact molecule **58** with diminished activity.

The IC_{50} and relative potency values of the most active compounds evaluated in this study are compared in Table IV. Although the compounds described above are only moderately active HMG-CoA reductase inhibitors, analysis of their intrinsic inhibitory activities suggests that inhibitor binding to HMG-CoA reductase is sensitive (a) to the stereochemistry of the lactone moiety, (b) to the ability of the lactone moiety to be opened to a dihydroxy acid, (c) to the length of the moiety bridging the lactone and the lipophilic groups, and (d) to the size and shape of the lipophilic group. Further modifications of the lipophilic group leading to more potent inhibitors will be described in subsequent papers from these Laboratories.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. 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 analysis for carbon, hydrogen, and nitrogen

Scheme I



[a] $\overline{CH}_2COC\overline{H}_2CO_2CH_3$. [b] H^+. [c] OH^-. [d] $NaBH_4$, EtOH. [e] $C_6H_5CH_3$, Δ. [f] H_2, Rh/C. [g] Dibal. [h] CH_3OH, PPTS. [i] NH_3. [j] (*R*)-(+)-$C_6H_5CH(CH_3)NH_2$.

Table IV. In Vitro Inhibitory Potencies against HMG-CoA Reductase

no.	IC_{50},[a,b] μM	rel potency[a]
compactin	0.01	100
6a(±)	22	0.08
6a(+)	10.8	0.16
7	15.2	
13a	20	0.09
16	19.8	0.08
47	129	
51	107	
52	90	
55	1.9	1.1
56	0.89	1.5
57	1.6	0.9

[a] Relative precision is ±10%. [b] IC_{50} is the micromolar concentration of the inhibitor required to give 50% inhibition under the conditions of the assay system.

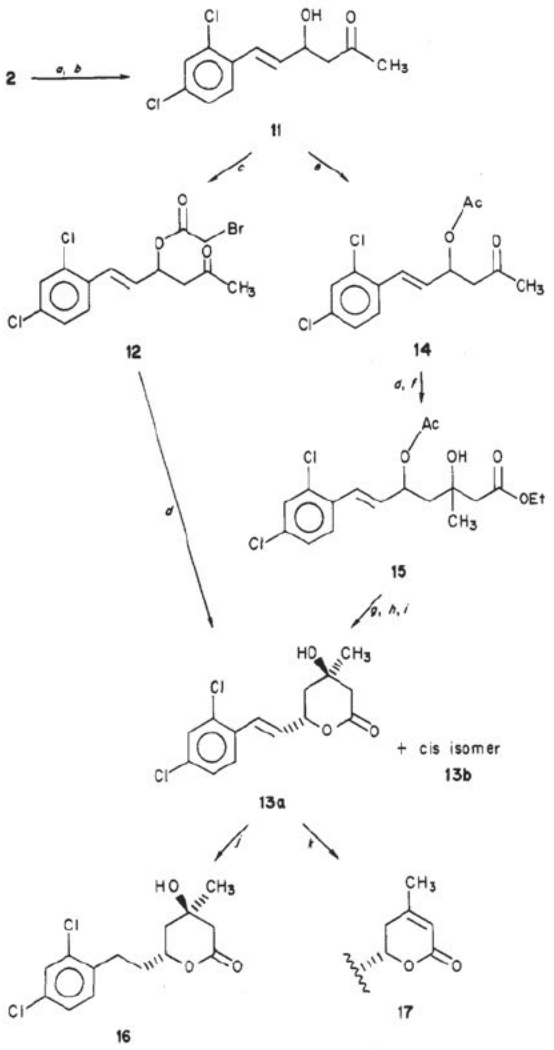
were determined with a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise. Optical rotations were determined with a Perkin-Elmer Model 141 polarimeter. All starting materials were commercially available unless indicated otherwise.

3-(2,4-Dichlorophenyl)-2-propenal (2) was prepared by modification of the procedure of Baker.[23] A solution of NaOH (0.125 g) in CH_3OH (2 mL) was added dropwise to a stirred suspension of 2,4-dichlorobenzaldehyde (7.5 g, 0.043 mol) in acetaldehyde (30 mL) cooled in an ice bath. The resulting solution was stirred 30 min with cooling, diluted with acetic anhydride (25 mL), and heated at 120 °C for 1 h. This mixture was cooled, diluted with H_2O (60 mL) and 6 N HCl (25 mL), and heated at 100 °C for 0.5 h. The light brown, oily product solidified upon cooling. It was collected, dried, and triturated with Et_2O to provide **2** (8.5 g, 98%), mp 106–108 °C. An analytical sample was prepared by recrystallization from hexane to provide **2** as a pale yellow solid: mp 107–108 °C; NMR δ 6.70 (H, dd, *J* = 15, 6 Hz), 7.20–7.73 (3 H, m), 7.87 (H, d, *J* = 15 Hz), 9.8 (H, d, *J* = 6 Hz). Anal. ($C_9H_6Cl_2O$) C, H.

Methyl (*E*)-7-(2,4-dichlorophenyl)-5-hydroxy-3-oxo-6-heptenoate (3) was prepared by a modification of the procedure of Weiler.[16] Methyl acetoacetate (23.2 g, 0.2 mol) was added dropwise to a stirred suspension of sodium hydride (50% oil suspension) (10.5 g, 0.22 mol) in anhydrous THF (500 mL) at 0 °C under a N_2 atmosphere. The resulting solution was stirred 15 min at 0 °C and then treated with a 2.2 M solution (95.4 mL, 0.21 mol) of *n*-butyllithium in hexane over 10 min. The yellow solution was stirred 15 min at 0 °C and then was treated with a solution of **2** (44.2 g, 0.22 mol) in anhydrous THF (250 mL). The resulting orange solution was stirred 15 min at 0 °C and then quenched by dropwise addition of 12 N HCl (48 mL). The reaction mixture was diluted with H_2O (300 mL) and extracted with Et_2O (3 × 300 mL). The organic extracts were combined, washed with brine (2 × 200 mL), dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo, leaving a red oil. The red oil was stirred in petroleum ether (200 mL) in order to remove the mineral oil. The mixture was cooled and the petroleum ether decanted to provide 62.8 g (90%) of **3**: NMR δ 2.83 (2 H, d, *J* = 6 Hz), 3.47

(23) Baker, B. R.; Janson, E. E.; Vermeulen, N. M. J. *J. Med. Chem.* **1969**, *12*, 898.

Scheme II



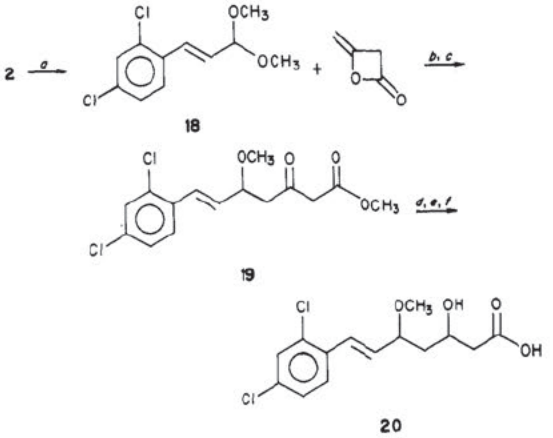
[a] (n-Bu)$_3$SnOCH$_3$, CH$_2$=C(OAc)CH$_3$. [b] HO$_2$CCO$_2$H. [c] BrCH$_2$COBr, C$_5$H$_5$N. [d] Zn, CuBr, Et$_2$AlCl. [e] Ac$_2$O, C$_5$H$_5$N. [f] BrCH$_2$CO$_2$Et. [g] OH$^-$. [h] H$^+$. [i] Δ, C$_6$H$_5$CH$_3$. [j] H$_2$, Rh/C. [k] PTSA, C$_6$H$_5$CH$_3$, Δ.

(2 H, s), 3.70 (3 H, s), 4.76 (H, m), 6.13 (H, dd, J = 15, 6 Hz), 6.90 (H, d, J = 15 Hz), 7.0–7.5 (3 H, m).

(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-5,6-dihydro-4-hydroxy-2*H*-pyran-2-one (4). The ester **3** (2.0 g, 6.3 mmol) was stirred in 0.1 N NaOH (200 mL) for 4 h. The resulting solution was acidified with 6 N HCl to provide a yellow solid which was recrystallized to analytical purity: yield 0.93 g; NMR (Me$_2$SO-d_6) δ 2.60 (2 H, m), 5.00 (H, s), 5.13 (H, m), 4.67 (H, dd, J = 15, 6 Hz), 6.97 (H, d, J = 15 Hz), 7.27–7.87 (3 H, m), 11.5 (H, br s).

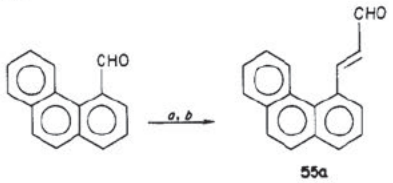
Methyl (*E*)-7-(2,4-Dichlorophenyl)-3,5-dihydroxy-6-heptenoate (5). Sodium borohydride (1.3 g, 33.7 mmol) was added with stirring to a cooled solution (5 °C) of **3** (10.7 g, 33.7 mmol) in EtOH (100 mL) at a rate sufficient to maintain the internal temperature at 15–20 °C. The resulting solution was stirred an additional 2 h with ice-bath cooling and then acidified with 6 N HCl. The resulting mixture was diluted with H$_2$O (250 mL) and extracted with Et$_2$O (3 × 200 mL). The Et$_2$O extracts were combined, washed with brine, dried over MgSO$_4$, and filtered. The filtrate was evaporated in vacuo to provide a yellow oil (10.4 g, 97%). A portion of the oil was purified by medium-pressure chromatography on a 25 × 1000 mm silical gel column. Elution

Scheme III



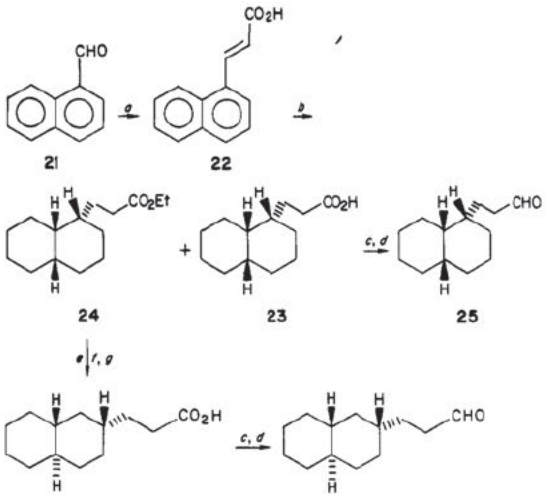
[a] MeOH, PTSA. [b] TiCl$_4$. [c] MeOH. [d] NaBH$_4$. [e] OH$^-$. [f] H$^+$.

Scheme IV



[a] LiCH=CHOC$_2$H$_5$. [b] Silica gel.

Scheme V

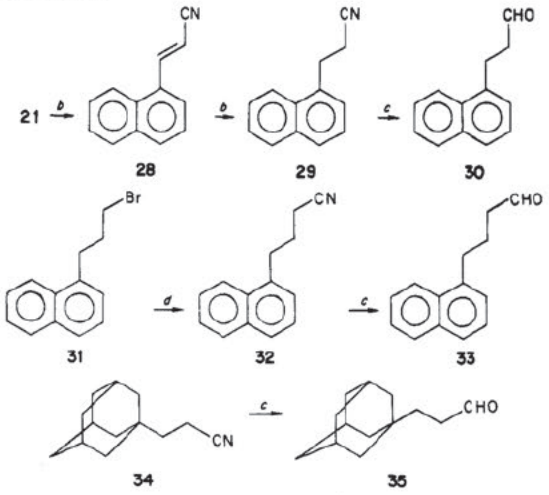


[a] CH$_2$(CO$_2$H)$_2$, C$_5$H$_5$N. [b] H$_2$, Ru/C, EtOH. [c] SOCl$_2$. [d] H$_2$, Pd/C, 2,6-(Me)$_2$C$_5$H$_3$N. [e] AlCl$_3$. [f] OH$^-$. [g] H$^+$.

with CH$_2$Cl$_2$–CH$_3$OH (49:1, v/v; 500 mL) provided a forerun which was discarded. Continued elution with the same eluant (3500 mL) provided **5** as a yellow oil; NMR δ 1.60–1.93 (2 H, m), 2.50 (2 H, d, J = 6 Hz), 3.67 (3 H, s), 4.13–4.77 (2 H, m), 5.93–6.40 (H, m), 6.93 (H, d, J = 15 Hz), 7.17–7.50 (3 H, m). Anal. (C$_{14}$H$_{16}$Cl$_2$O$_4$) H; C: calcd, 52.68; found, 52.25.

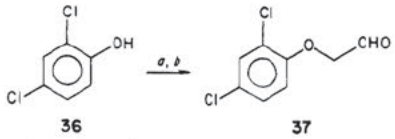
(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (6a(±) and 6b(±)). An EtOH solution (100 mL) containing **5** (8.4 g, 26.3 mmol) and 1 N NaOH

Scheme VI



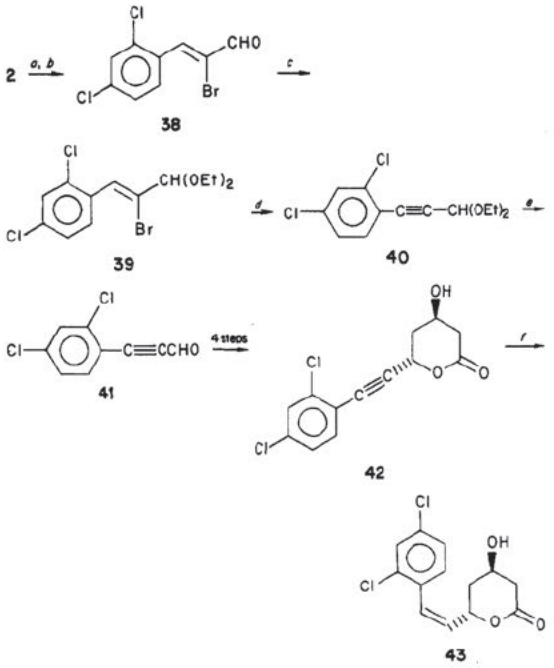
[a] $NCCH_2CO_2H$, NH_4OAc, C_5H_5N. [b] H_2, Pd/C. [c] Dibal. [d] NaCN.

Scheme VII



[a] $BrCH_2CH(OEt)_2$. [b] 2N H_2SO_4.

Scheme VIII



[a] Br_2. [b] K_2CO_3. [c] $(EtO)_3CH$, NH_4Cl. [d] KOH. [e] Dilute H_2SO_4. [f] 5% $Pd/CaCO_3$.

(26.3 mL) was stirred at ambient temperature for 1 h. The reaction solution was acidified with 6 N HCl, diluted with H_2O (200 mL), and extracted with Et_2O (3 × 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated in vacuo to provide a mixture of acid and lactone (7.8 g, 97%). A solution of this mixture in toluene (100 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). The solution was refluxed for an additional 4 h and then the toluene was removed in vacuo leaving a yellow oil (7.2 g, 95%) which was a mixture of **6a(±)** and **6b(±)**. The oil was chroamtographed on a silica gel column (500 g). Elution with CH_2Cl_2–acetone (4:1, v/v; 900 mL) provided a forerun which was discarded. Continued elution with the same eluant (300 mL) gave the trans isomer **6a(±)** (2.5 g). Recrystallization of the solid provided an analytical sample, as colorless needles: NMR (acetone-d_6) δ 2.06 (2 H, m), 2.69 (2 H, m), 4.43 (H, m), 5.42 (H, m), 6.49 (H, dd, J = 15, 6 Hz), 7.08 (H, d, J = 15 Hz), 7.33–7.59 (2 H, m), 7.79 (H, d, J = 8 Hz). An isomeric purity of 99.8% was determined for **6a(±)** by HPLC on a Whatman Partisil-5 RAC column with 15% 2-propanol/hexane as the eluant. The time of elution was 4.96 min at a flow rate of 6 mL/min.

Further elution of the column with the same eluant (600 mL) gave the cis isomer **6b(±)** as a solid (1.25 g). Recrystallization gave an analytical sample as colorless needles: NMR (acetone-d_6) δ 1.50–2.93 (4 H, m), 4.36 (H, m), 5.02 (H, m), 6.37 (H, dd, J = 15, 6 Hz), 7.02 (H, d, J = 15 Hz), 7.16–7.50 (2 H, m), 7.67 (H, d, J = 8 Hz). An isomeric purity of 99.3% was determined for **6b(±)** by HPLC on a Whatman Partisil-5 RAC column with 15% 2-propanol/hexane as the eluant. The time of elution was 5.79 min at a flow rate of 6 mL/min.

***trans*-6-[2-(2,4-Dichlorophenyl)ethyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (7).** A solution of **6a(±)** (1.5 g, 5.2 mmol) in THF (100 mL) was stirred magnetically and hydrogenated at room temperature under atmospheric pressure in the presence of 5% rhodium on carbon (150 mg) until 1.25 molar equiv of hydrogen had been consumed. After removal of the catalyst by filtration, the filtrate was evaporated in vacuo, leaving a solid. The solid was recrystallized to provide **7** (0.9 g): NMR δ 1.67–2.17 (4 H, m), 2.60–3.13 (4 H, m), 4.30–4.50 (H, m), 4.57–4.90 (H, m), 7.14–7.44 (3 H, m).

Resolution of (±)-*trans*-(*E*)-6-[2-(2,4-Dichlorophenyl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (6a). A solution of **6a(±)** (2.87 g, 10 mmol) in (*R*)-(+)-α-methylbenzylamine (15 mL) was stirred for 18 h at ambient temperature and then poured into H_2O (100 mL). This aqueous mixture was acidified with 6 N HCl and extracted with Et_2O (3 × 100 mL). The Et_2O extracts were combined, washed with brine, dried over $MgSO_4$, and filtered. Evaporation of the filtrate in vacuo provided the crude diastereomeric amides as a tan viscous oil (4.1 g, 100%).

This oil (3.1 g, 7.6 mmol) was chromatographed on a silica gel column (200 g). Elution with acetone–CH_2Cl_2 (1:4, v/v; 1200 mL) gave a forerun which was discarded. Continued elution with the same eluant provided the mixture of diastereomeric amides as a viscous oil (3.0 g, 97%). This mixture was separated by chromatography on a Waters Prep LC 500. The separation was accomplished by using two Prep PAK-500 silica cartridges in series and eluting with acetone–CH_2Cl_2 (1:4, v/v). Use of the shave–recycle technique provided diastereomer A (1.36 g) and diastereomer B (1.2 g).

Recrystallization of diastereomer A from *n*-butyl chloride gave colorless clusters (1.0 g) which melted at 106–108 °C; NMR δ 1.47 (3 H, d, J = 6 Hz), 1.70 (2 H, m), 2.33 (2 H, d, J = 6 Hz), 4.30 (H, m), 4.58 (H, m), 5.13 (H, m), 6.20 (H, dd, J = 15, 6 Hz), 6.33 (H, m), 6.93 (H, d, J = 15 Hz), 7.33 (8 H, m). Anal. ($C_{21}H_{23}Cl_2NO_3$) C, H, N.

Recrystallization of diastereomer B from *n*-butyl chloride gave a pale yellow solid which melted at 55–60 °C: NMR δ 1.47 (3 H, d, J = 6 Hz), 1.70 (2 H, m), 2.33 (2 H, d, J = 6 Hz), 4.33 (H, m), 4.60 (H, m), 5.16 (H, m), 6.17 (H, dd, J = 15, 6 Hz), 6.23 (H, m), 6.93 (H, d, J = 15 Hz), 7.33 (8 H, m). Anal. ($C_{21}H_{23}Cl_2NO_3$) C, H, N.

(+)-*trans*-(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (6a(+)). Diastereomer A (0.74 g, 1.8 mmol) was dissolved in 95% ethanol (25 mL) containing 1 N NaOH (3.6 mL, 3.6 mmol) and the solution was refluxed for 54 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 Et_2O. The Et_2O extracts were combined, washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated, leaving the intermediate acid as a yellow oil (0.54 g). A solution of the oil in toluene (150 mL) was refluxed through a Soxhlet containing molecular sieves (3 Å) for 5 h. The solution was evaporated in vacuo, leaving the lactone **6a(+)** as a yellow solid. Recrystallization gave colorless needles (0.13 g): $[\alpha]^{25}_D$ +5.9° (c 0.425, $CHCl_3$); NMR δ 2.03 (2 H, m), 2.73 (2 H, m), 4.46 (H, m), 5.41 (H, m), 6.19 (H, dd, J = 15, 6 Hz), 7.01 (H, d, J = 15 Hz), 7.14–7.50 (3 H, m).

(−)-*trans*-(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (6a(−)). Diastereomer B (1.1 g, 2.7 mmol) was dissolved in 1 N NaOH (5.4 mL, 5.4 mmol) and the solution was refluxed for 18 h. The same workup and lactonization used in the synthesis of **6a(+)** gave **6a(−)** as a yellow solid. Recrystallization provided colorless needles (0.34 g): mp 114–115 °C; $[\alpha]^{25}_D$ −6.6° (c 0.555, $CHCl_3$); NMR δ 2.03 (2 H, m), 2.73 (2 H, m), 4.46 (H, m), 5.41 (H, m), 6.19 (H, dd, J = 15, 6 Hz), 7.01 (H, d, J = 15 Hz), 7.14–7.50 (3 H, m). The optical purities of **6a(+)** and **6a(−)** were determined by NMR with ca. 0.5 molar equiv of Eu(hfbc)$_3$ in $CDCl_3$; each enantiomer was found to be free of the other enantiomer within the limits of detection (threshold = ca. 2%). Therefore, the optical purity of **6a(+)** and **6a(−)** was estimated to be 98 ± 2%.

(2*R,4*R**,6*S**)- and (2*S**,4*R**,6*S**)-(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydropyran (8 and 9).** A solution of Dibal (0.89 M) in hexane (4.31 mL, 3.83 mmol) was added dropwise over 10 min to a stirred toluene (20 mL) and THF (10 mL) solution of **6a(±)** (0.5 g, 1.74 mmol) which was cooled to −78 °C. After stirring another 30 min at −78 °C, the reaction was quenched by the addition of MeOH (613 mg, 19.15 mmol). After the reaction mixture had warmed to ambient temperature, it was diluted with H_2O (1 mL), treated with Celite, and stirred for an additional 15 min. Anhydrous Na_2SO_4 was added and stirring was continued another 15 min. This mixture was filtered and the filtrate evaporated in vacuo to provide a mixture of lactols (0.5 g, 99%). A CH_3OH (10 mL) solution of the lactol mixture (0.25 g, 0.86 mmol) was treated with PPTS (25 mg) and then refluxed through a Soxhlet containing molecular sieves (3 Å). The reaction was cooled and diluted with Et_2O (200 mL). After washing with saturated $NaHCO_3$ solution, H_2O and brine, the organic layer was dried over $MgSO_4$ and filtered. The filtrate was evaporated in vacuo to provide the mixture of **8** and **9** (255 mg, 78%).

This mixture was separated by flash chromatography an a silica column. Elution with CH_2Cl_2–acetone (19:1, v/v) first provided the minor isomer **9** followed by the major isomer **8**.

Isomer **9**: NMR δ 1.47–2.13 (4 H, m), 3.44 (3 H, s), 3.53 (H, m), 4.13 (H, m), 4.77 (H, m), 6.20 (H, dd, J = 15, 6 Hz), 6.98 (H, d, J = 15 Hz), 7.13–7.57 (3 H, m).

Isomer **8**: NMR δ 1.47–1.93 (4 H, m), 3.53 (3 H, s), 4.40 (H, m), 4.63 (H, m), 4.85 (H, dd, J = 9, 3 Hz), 6.23 (H, dd, J = 15, 6 Hz), 6.98 (H, d, J = 15 Hz), 7.10–7.57 (3 H, m).

***erythro*-(*E*)-7-(2,4-Dichlorophenyl)-3,5-dihydroxy-6-heptenamide (10).** Lactone **6a(±)** (6.0 g, 20.9 mmol) was dissolved in dry MeOH (100 mL) and saturated with anhydrous NH_3 at 0 °C. The reaction was sealed and stirred at room temperature for 13 h, stored in the freezer overnight, and then worked up by evaporation under reduced pressure. Two recrystallizations from acetone–hexane gave **10** (4.0 g): mp 117–118 °C; NMR δ 1.72 (2 H, m), 2.40 (2 H, d, J = 6 Hz), 4.22 (1 H, m), 4.55 (1 H, m), 5.00 (2 H, t, J = 5 Hz), 6.17 (1 H, d, J = 7 Hz), 6.35 (1 H, d, J = 7 Hz), 6.8–7.75 (3 H, m).

6-(2,4-Dichlorophenyl)-4-hydroxy-5-hexen-2-one (11). 2-Acetoxypropene (3.3 mL, 30 mmol) and tri-*n*-butyltin methoxide (5.7 g, 24 mmol) were combined and stirred at 60–70 °C under N_2 for 1 h and then placed under vacuum for an additional 30 min. Propenal **2** (4 g, 20 mmol) was added and the reaction mixture was stirred at 70 °C under N_2 for 4 h. The clear reaction mixture was then cooled, treated with malonic acid (1 g, 10 mmol) in Et_2O (20 mL), and refluxed for 30 min. After cooling to −20 °C, the reaction mixture was filtered and the precipitate was washed with Et_2O (4 × 10 mL). The Et_2O solutions were combined and evaporated, and the residual oil was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (99:1, v/v; 2 L) provided **11** as a thick yellow oil (4.2 g, 81%); NMR δ 2.2 (3 H, s), 2.73 (2 H, d, J = 6 Hz), 4.73 (H, m), 6.10 (H, dd). Anal. ($C_{12}H_{12}Cl_2O_2$) C, H.

6-(2,4-Dichlorophenyl)-2-oxo-5-hexen-4-yl 2-Bromoacetate (12). 2-Bromoacetyl bromide (1.1 mL, 13.2 mmol) was added dropwise to a stirred solution of **11** (3.4 g, 13.1 mmol) and pyridine (1.07 mL, 13.2 mmol) in Et_2O (100 mL) at 0 °C. The ice bath was removed and the reaction mixture was stirred at 20 °C for 2 h and then diluted with H_2O (100 mL). The organic layer was separated and washed with 1 N HCl (100 mL), H_2O (2 × 100 mL), and saturated brine, dried ($MgSO_4$), filtered, and evaporated. The residual oil was chromatographed on silica gel. Elution with CH_2Cl_2–acetone (99:1, v/v; 1.9 L) provided **12** (2.8 g, 56%): NMR δ 2.2 (3 H, s), 2.92 (2 H, t, J = 7 Hz), 3.85 (2 H, s), 5.9 (H, m), 6.15 (H, m), 6.95–7.5 (4 H, m). Replacement of pyridine with an equivalent of TEA provided only the dienone (6-(2,4-dichlorophenyl)hexa-3,5-dien-2-one) as a yellow powder (77%): mp 80–82 °C; NMR δ 2.28 (3 H, s), 6.15 (H, d, J = 15 Hz), 6.7–7.6 (6 H, m).

(*E*)-6-[2-(2,6-Dichlorophenyl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-4-methyl-2*H*-pyran-2-one (13). A solution of **12** (2.8 g, 7.4 mmol) in dry THF (50 mL) was added dropwise to a vigorously stirred slurry of activated Zn dust (720 mg, 11.1 mmol), CuBr (60 mg, 0.4 mmol), Et_2AlCl (25% solution in toluene; 3.2 mL, 8 mmol), and dry THF (50 mL) under N_2 at 20 °C. Stirring was continued for 5 h before quenching with pyridine (8 mL) followed by H_2O (500 mL) addition and Et_2O extraction (3 × 150 mL). The combined Et_2O extracts were washed with 1 N HCl (2 × 50 mL), H_2O (2 × 250 mL), and saturated brine, dried ($MgSO_4$), filtered, and evaporated, leaving a sticky, pale yellow solid (1.8 g) which was a mixture of **13a** and **13b**. This crude product was digested once with Et_2O (40 mL) and then crystallized from *n*-butyl chloride (25 mL) to provide the trans isomer **13a** as tiny colorless crystals (550 mg): mp 136–138 °C; NMR δ 1.4 (3 H, s, CH_3), 1.73 (5-H_a, dd, J = 11, 13 Hz), 2.06 (5-H_e, ddd, J = 2, 11, 13 Hz), 2.12 (H, s, OH), 2.45 (3-H_a, d, J = 18 Hz), 2.73 (3-H_e, dd, J = 2, 18 Hz), 5.2–5.45 (6-H_a, m), 6.13 (H, dd, J = 15, 6 Hz), 6.92 (H, d, J = 15 Hz), 7.0–7.43 (3 H, m).

The filtrates from digestion and crystallization vide supra were combined, evaporated, and chromatographed with a Waters Prep LC 500. The separation was accomplished by using two prep PAK-500 silica cartridges in series and eluting with CH_2Cl_2–acetone (15:1, v/v). By use of the shave-recycle technique, the cis (**b**, 220 mg) and the trans (**a**, 230 mg) isomers of **13** were separated. The cis isomer (**13b**) was crystallized from *n*-butyl chloride–hexane (2:1, v/v) (120 mg): mp 135–137 °C; NMR δ 1.46 (3 H, s, CH_3), 1.8–2.4 (3 H, m, 5-$H_{a,e}$, OH), 2.65 (2H, s, 3-$H_{a,e}$), 4.8–5.1 (6-H_a, m), 6.26 (H, dd, J = 15, 6 Hz), 7.03 (H, d, J = 15 Hz).

The epimeric alcohols were readily distinguished by analytical TLC (fluorescent silica gel (40 Å), 1 × 3 in., MK6F, Whatman) with CH_2Cl_2–acetone (9:1, v/v) as the eluant; R_f 0.25 for **13b** and 0.30 for **13a**.

Alternate Route to 13. 4-Acetoxy-6-(2,4-dichlorophenyl)-5-hexen-2-one (14). Acetyl chloride (1.2 mL, 16.5 mmol) was added dropwise to a stirred solution of **11** (3.9 g, 15 mmol) in pyridine (60 mL) cooled at 0 °C. The ice bath was removed and the reaction mixture was stirred at 20 °C for 2 h and then diluted with Et_2O (300 mL). The Et_2O solution was washed with 1 N HCl (3 × 300 mL) and saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and evaporated. The residual pale amber oil (4.1 g) was chromatographed on silica gel. Elution with CH_2Cl_2 (2 L) provided **14** as a pale yellow oil (3.95 g, 87%); NMR δ 2.03 (3 H, s), 2.17 (3 H, s), 2.83 (2 H, dd, J = 7, 2 Hz). Anal. ($C_{14}H_{14}Cl_2O_3$) C, H.

Ethyl 5-Acetoxy-7-(2,4-dichlorophenyl)-3-hydroxy-3-methyl-6-heptenoate (15). A solution of **14** (1.3 g, 4.3 mmol) and ethyl bromoacetate (0.47 mL, 4.2 mmol) in dry THF (10 mL) was added dropwise to a vigorously stirred slurry of activated Zn dust (490 mg, 7.5 mmol), CuBr (29 mg, 0.2 mmol), Et_2AlCl (25% solution in toluene; 1.72 mL, 4.3 mmol), and dry THF (5 mL) under N_2 at 20 °C. Stirring was continued for 5 h before quenching with pyridine (3.5 mL) followed by H_2O (50 mL) addition and Et_2O extraction (3 × 80 mL). The combined Et_2O extracts were washed with 1 N HCl (2 × 25 mL), H_2O (2 × 50 mL), and saturated brine, dried ($MgSO_4$), filtered, and evaporated, leaving crude **15** as a pale yellow oil (1.2 g, 75%); NMR δ 1.28 (3 H, t, J = 7 Hz), 1.33 (3 H, s), 2.10 (3 H, s), 2.45 (2 H, d, J =

13 Hz), 4.16 (2 H, q, J = 7 Hz).

Compound 13. This compound was prepared similarly to **6**. With **15** (1.2 g, 3.2 mmol) as starting material, **13** (120 mg) was obtained as a mixture of trans (54%) and cis (46%) isomers as determined by HPLC (Whatman Partisil-10 PAC eluting with *i*-PrOH–hexane (1:10, v/v) at 2.1 mL/min). Times of elution are 3.0 min for **a** and 4.0 min for **b**.

***trans*-6-[2-(2,6-Dichlorophenyl)ethyl]-3,4,5,6-tetrahydro-4-hydroxy-4-methyl-2*H*-pyran-2-one (16).** This compound was prepared analogously to **7**, starting with **13a** (100 mg, 0.33 mmol). The residual oil was chromatographed on silica gel. Elution with CH_2Cl_2–acetone (19:1, v/v; 350 mL) provided **16** (50 mg, 50%): NMR δ 1.37 (3 H, s), 1.6–2.1 (4 H, m), 2.5–3.1 (4 H, m), 4.55–4.90 (H, m), 7.15–7.25 (2 H, m), 7.33–7.43 (H, m).

(*E*)-6-[2-(2,4-Dichlorophenyl)ethenyl]-5,6-dihydro-4-methyl-2*H*-pyran-2-one (17). A solution of **13a** (150 mg, 0.5 mmol) in toluene (75 mL) containing PTSA (5 mg) was refluxed through a Soxhlet filled with 3-Å molecular sieves for 6 h. After evaporation of the toluene, the residue was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (99:1, v/v; 60 mL) provided **17** (130 mg, 90%): mp 108–110 °C; NMR δ 2.0 (3 H, s), 2.4–2.6 (2 H, m), 5.0–5.25 (H, m), 5.85–6.0 (H, m), 6.25 (H, dd, J = 16, 6 Hz), 6.95–7.6 (4 H, m).

2,4-Dichlorocinnamaldehyde Dimethyl Acetal (18). A solution of **2** (10 g, 50 mmol), PTSA (50 mg), and anhydrous MeOH (100 mL) was refluxed through a Soxhlet filled with 3-Å molecular sieves for 1 h. The solution was cooled, treated with anhydrous K_2CO_3, filtered, and evaporated. The residual oil was chromatographed on silica gel. Elution with CH_2Cl_2 provided **18** as a clear, pale brown oil (10.4 g, 84%).

Methyl 7-(2,4-Dichlorophenyl)-5-methoxy-3-oxo-6-heptanoate (19). A solution of $TiCl_4$ in CH_2Cl_2 (3 M, 10 mL, 30 mmol) was added dropwise to a vigorously stirred solution of **18** (6.18 g, 25 mmol) in CH_2Cl_2 (40 mL) at −78 °C under N_2. A solution of diketene in CH_2Cl_2 (5 M, 10 mL, 50 mmol) was added in a steady stream. The dark reaction mixture was stirred at −78 °C for 1 h and then anhydrous MeOH (20 mL) was added. After stirring for an additional 30 min at −20 °C, the light yellow solution was poured into cold, aqueous K_2CO_3 (10 g/L). The yellow salts were separated by filtration and washed with CH_2Cl_2. The organic layers were combined, washed with H_2O and saturated brine, dried ($MgSO_4$), and evaporated, leaving **19** as an orange oil (6.6 g, 80%) which exhibited one major spot (R_f 0.45) on TLC (fluorescent silica gel (40 Å), 1 × 3 in. MK6F, Whatman) after eluting with CH_2Cl_2–MeOH (99:1, v/v): NMR δ 2.90 (2 H, d, J = 4 Hz), 3.43 (3 H, s), 3.63 (2 H, s), 3.83 (3 H, s), 4.13–4.57 (H, m), 6.10 (H, dd, J = 15, 7 Hz), 6.83–7.43 (4 H, m).

3-(*cis-syn*-Decahydro-1-naphthalenyl)propanoic Acid (23) and Ethyl Ester 24. 3-(1-Naphthalenyl)acrylic acid[24] (79.6 g, 400 mmol) was hydrogenated in EtOH (600 mL) over 5% Ru on carbon (8.0 g) at 100 °C and 3000 psi. The catalyst was removed by filtration and the filtrate was evaporated. The residue was distributed between Et_2O (700 mL) and 5% NaOH (2 × 400 mL). The Et_2O layer was washed with H_2O and saturated brine, dried ($MgSO_4$), filtered, and evaporated. Distillation of the residue provided ethyl ester **24** as a clear colorless liquid (48.4 g, 50.7%): bp 120–122 °C (1.0 mm); NMR δ 1.0–1.9 (22 H, m), 2.27 (2 H, t, J = 6 Hz), 4.14 (2 H, q, J = 6 Hz). Anal. ($C_{15}H_{26}O_2$) C, H.

The basic layer vide supra was extracted with Et_2O (200 mL) and then acidified with 12 N HCl after cooling to 0 °C. The acid was removed by filtration and crystallized from petroleum ether to provide **23** as colorless needles (23.2 g, 27.6%): mp 80–82 °C; NMR δ 0.8–1.8 (19 H, m), 2.33 (2 H, t, J = 8 Hz), 11.4 (H, br s). Anal. ($C_{13}H_{22}O_2$) C, H.

3-(*cis-syn*-Decahydro-1-naphthalenyl)propanal (25). Propanoic acid (**23**) (10 g, 47.6 mmol) was dissolved in $SOCl_2$ (20 mL) and the solution was heated at reflux for 3.5 h. The solution was evaporated and the residual oil was distilled in vacuo to provide the acid chloride as a clear colorless oil (7 g, 64%): bp 113–120 °C (0.8–1.0 mm); NMR δ 1.0–2.0 (19 H, m), 2.87 (2 H, t, J = 8 Hz). Anal. ($C_{13}H_{21}ClO$) C, H.

The acid chloride (4.56 g, 20 mmol) was added dropwise to a well-stirred suspension of hydrogen-equilibrated 10% Pd/C (200 mg) under hydrogen in dry THF (80 mL) containing 2,6-dimethylpyridine (2.14 g, 20 mmol). Hydrogen uptake occurred at a steady rate and was complete in 1 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was distributed between 5% HCl (200 mL) and Et_2O (200 mL). The Et_2O was washed with aqueous $NaHCO_3$, H_2O, and saturated brine, dried ($MgSO_4$), filtered, and evaporated. The residue was distilled in vacuo to provide **25** as a clear colorless oil (2.7 g, 69.5%): bp 96–99 °C (0.5 mm); NMR δ 1.0–2.0 (19 H, m), 2.50 (2 H, dt, J = 8, 1 Hz), 9.8 (H, t, J = 1 Hz). Anal. ($C_{13}H_{22}O$) H; C: calcd, 80.35; found, 79.70.

3-(*trans-syn*-Decahydro-2-naphthalenyl)propanoic Acid (26). Ethyl propanoate (**24**) (24 g, 100 mmol) was mixed with anhydrous $AlCl_3$ (27 g, 200 mmol) at 0 °C and then stirred at 20 °C for 70 h. The viscous reaction mixture was cooled to 0 °C, quenched with ice-cold 1 N HCl (500 mL), and extracted with Et_2O (4 × 100 mL). The Et_2O extracts were combined and evaporated to afford a residue which was stirred with 1 N NaOH (100 mL, 100 mmol) and MeOH (400 mL) for 2 h at 20 °C. The reaction mixture was evaporated and the residue was distributed between H_2O (200 mL) and Et_2O (200 mL). The aqueous layer was cooled to 0 °C and acidified with 12 N HCl to provide **26** as a sticky yellow solid. Recrystallization from petroleum ether gave 9.1 g (43%), mp 98–98.5 °C. Anal. ($C_{13}H_{22}O_2$) C, H.

3-(*trans-syn*-Decahydro-2-naphthalenyl)propanal (27). This compound was prepared similarly to **25**, starting with **26** (10.1 g, 48 mmol). The intermediate acid chloride was obtained as a clear colorless liquid (10.2 g, 93%): bp 113–116 °C (0.8–1.0 mm); NMR δ 0.6–1.9 (19 H, m), 2.88 (2 H, t, J = 9 Hz). Anal. ($C_{13}H_{21}ClO$) C, H. Reduction provided **27** (74%): bp 107–112 °C (1.3–1.5 mm); NMR δ 0.5–1.8 (19 H, m), 2.43 (2 H, dt, J = 8, 1 Hz), 9.85 (H, t, J = 1 Hz). Anal. ($C_{13}H_{22}O$) H; C: calcd, 80.35; found, 79.94.

(*E*)-3-(1-Naphthalenyl)propenenitrile (28). A mixture of 1-naphthaldehyde (156 g, 1.0 mol), cyanoacetic acid (78 g, 0.9 mol), and ammonium acetate (3 g) in toluene (200 mL) and pyridine (100 mL) was heated at reflux for 2 days; water was collected in a Dean–Stark trap. After evaporation of the solvents, the product was obtained by distillation in vacuo (~140–185 °C, 0.7 mm). Recrystallization from EtOH–H_2O gave **28** (145.7 g, 88%): mp 69–71 °C; NMR δ 5.94 (1 H, d, CH, J = 17 Hz), 7.25–8.1 (7 H, m, $C_{10}H_7$), 8.25 (1 H, d, CH, J = 17 Hz). Anal. ($C_{13}H_9N$) C, H, N.

3-(1-Naphthalenyl)propanenitrile (29). A mixture of **28** (17.9 g, 0.1 mol) and 5% Pd/C (1.0 g) in EtOH (200 mL) was hydrogenated in a Parr apparatus. After filtration and removal of the solvent, the product was obtained by distillation in vacuo (~150–165 °C, 0.5 mm). Recrystallization from Et_2O–petroleum ether afforded **29** (16.4 g, 90%): mp 48–51 °C; NMR δ 2.72 (2 H, t, J = 8 Hz), 3.4 (2 H, t, J = 8 Hz), 7.25–8.1 (7 H, m). Anal. ($C_{13}H_{11}N$) C, H, N.

3-(1-Naphthalenyl)propanal (30). To a stirred suspension of **29** (21.7 g, 0.12 mol) in Et_2O (400 mL) at −78 °C under N_2 was added a solution of Dibal (85 mL, 0.128 mol) in toluene (25.3%, 0.8446 g/mL) over a period of 1 h. After an additional 1 h at −78 °C, the dry ice–acetone bath was removed and the reaction mixture was stirred at room temperature for 3 h. The mixture was added slowly to 5% aqueous H_2SO_4 and then extracted with Et_2O. The Et_2O solution was dried and evaporated and the residual oil distilled to give the product as a colorless oil, bp 113–117 °C (0.2 mm), which solidified on standing. Recrystallization from Et_2O–petroleum ether yielded **30** (15.8 g, 72%): mp 29–31 °C; NMR δ 2.82 (2 H, m), 3.4 (2 H, t, J = 8 Hz), 7.21–8.02 (7 H, m), 9.86 (1 H, t, J = 1 Hz). Anal. ($C_{13}H_{12}O$) C, H.

4-(1-Naphthalenyl)butanenitrile[25] (32). A mixture of **31**[26] (58.8 g, 0.24 mol) and sodium cyanide (25 g, 0.5 mol) in EtOH (300 mL) and H_2O (100 mL) was heated at reflux with stirring for 5 h. The reaction mixture was cooled, concentrated in vacuo, and extracted with Et_2O. The Et_2O solution was dried, filtered, and concentrated to give the crude product, which was purified by distillation: yield 38.8 g (84%); bp 151–155 °C (0.3 mm); NMR

(24) West, B. L. *J. Am. Chem. Soc.* **1920**, *42*, 1656.

(25) UCLAF Fr. Patent 992104; *Chem. Abstr.* **1951**, *50*, P15591f.

(26) Rona, P.; Feldman, U. *J. Chem. Soc.* **1958**, 1737.

δ 1.7–2.3 (4 H, m), 3.08 (2 H, t, J = 7 Hz), 7.1–8.0 (7 H, m). Anal. ($C_{14}H_{13}H$) C, H, N.

4-(1-Naphthalenyl)butanal (33). This product was prepared from **32** in a manner similar to that used for **30** and purified by distillation: bp 123–126 °C (0.1 mm); NMR δ 2.13 (2 H, m), 2.50 (2 H, m), 3.12 (2 H, t, J = 8 Hz), 7.2–8.3 (7 H, m), 9.82 (1 H, t, J = 1 Hz).

3-(1-Adamantyl)propanal (35) was prepared analogously to **33** starting with **34**[27] (4.73 g, 25 mmol). Distillation under vacuum provided **35** as a colorless oil (2.7 g, 56%): bp 107–115 °C (1.0–1.6 mm) [lit.[28] bp 101–103 °C (1.5 mm)]; NMR δ 1.3–2.1 (17 H, m), 2.4 (2 H, dt, J = 9, 0.8 Hz), 9.85 (H, d, J = 0.8 Hz).

(2,4-Dichlorophenoxy)acetaldehyde (37) was prepared by the method of Julia and Tchernoff.[29]

(a) (2,4-Dichlorophenoxy)acetaldehyde diethyl acetal: yield (45%); bp 140–142 °C (2.2 mm) [lit.[29] bp 137–140 °C (2 mm)]; NMR δ 1.23 (6 H, t, J = 6 Hz), 3.43–3.93 (4 H, m), 4.0 (2 H, d, J = 4 Hz), 4.80 (H, t, J = 4 Hz), 6.67–7.3 (3 H, m).

(b) 37: yield (80%); bp 125–128 °C (2.2 mm) (lit.[29] bp 120 °C (1.5 mm)]; NMR δ 4.60 (2 H, s), 6.67–7.4 (3 H, m), 9.8 (H, s).

3-(2,4-Dichlorophenyl)-2-propynal (41) was synthesized from **2** by the procedure used by Allen and Edens[22] to convert 3-phenyl-2-propenal to 3-phenyl-2-propynal.

(a) (*Z*)-2-Bromo-3-(2,4-dichlorophenyl)-2-propenal (38): yield (67%). An analytical sample was crystallized from cyclohexane–toluene: mp 125–126 °C; NMR δ 7.35–7.65 (2 H, m), 8.2 (H, d, J = 6 Hz), 8.25 (H, s), 9.55 (H, s). Anal. ($C_9H_5BrCl_2O$) C, H.

(b) (*Z*)-2-Bromo-3-(2,4-dichlorophenyl)-2-propenal diethyl acetal (39): yield (70%); bp 130–140 °C (0.1–0.05 mm) as a pale yellow oil; NMR δ 1.25 (6 H, t, J = 6 Hz), 3.65 (4 H, dq, J = 6, 3 Hz), 5.0 (H, s), 7.2–7.75 (4 H, m).

(c) 3-(2,4-Dichlorophenyl)-2-propynal diethyl acetal (40): yield (88%); bp 122–124 °C (0.04 mm); NMR δ 1.23 (6 H, t, J = 6 Hz), 3.5–3.95 (6 H, m), 5.5 (H, s), 7.1–7.5 (3 H, m). Anal. ($C_{13}H_{14}Cl_2O_2$) C, H.

(d) 41: yield (67%). An analytical sample was crystallized from hexane: mp 57–58 °C; NMR δ 7.2–7.7 (3 H, m), 9.5 (H, s). Anal. ($C_9H_4Cl_2O$) C, H.

(*Z*)-3-(4-Phenanthrenyl)-2-propenal (55a) was prepared by the general procedure of Wollenberg.[30] *n*-Butyllithium (2.72 mmol) was added dropwise to a solution of *cis*-1-ethoxy-2-(tri-*n*-butylstannyl)ethylene[31] (2.3 g, 6 mmol) in dry THF (20 mL) at −78 °C. After stirring at −78 °C for 1 h, a solution of 4-phenanthrenecarboxaldehyde[32] (1.1 g, 5.3 mmol) in dry THF (10 mL) was added rapidly and the reaction mixture was stirred at −78 °C for an additional 2 min before removing the cooling bath. After stirring at 22 °C for 30 min, the reaction mixture was treated with saturated $NaHCO_3$ (20 mL) and the reaction mixture was distributed between Et_2O (100 mL) and H_2O (100 mL). The Et_2O layer was washed with H_2O (3 × 100 mL), dried ($MgSO_4$), filtered, and then evaporated. Chromatography of the biphasic residue on silica gel with elution by CH_2Cl_2 provided **55a** (900 mg, 73%): mp 112–120 °C. Crystallization from hexane yielded analytically pure **55a**: mp 125–129 °C; NMR δ 6.8 (H, dd, J = 18, 8 Hz), 7.5–8.45 (10 H, m), 9.9 (H, d, J = 8 Hz). Anal. ($C_{17}H_{12}O$) C, H.

Isolation of HMG-CoA Reductase. Male Holtzman Sprague–Dawley rats (225–250 g) were kept on reversed lighting and fed Purina rat chow containing 3% cholestyramine for 7 days preceding their sacrifice by CO_2 asphyxiation. Livers were removed 6 h into the dark cycle and used immediately to prepare microsomes. HMG-CoA reductase was solubilized from the freshly prepared microsome by the method of Heller and Shrewsbury[33] and purified through the second ammonium sulfate precipitation step as described by Kleinsek et al.[34] The enzyme preparation was tested for HMG-CoA reductase potency and diluted with 100 mM phosphate buffer (pH 7.2) so that 100 μL of the enzyme solution, when added to the assay control, gave a value of 50000–60000 dpm. The enzyme preparation was stored at −80 °C.

HMG-CoA Reductase Inhibition Assay. The assay is essentially the procedure of Shefer et al.[35] The complete assay medium contained the following in a total volume of 0.8 mL: phosphate buffer, pH 7.2, 100 mM; $MgCl_2$, 3 mM; NADP, 3 mM; glucose 6-phosphate, 10 mM; glucose-6-phosphate dehydrogenase, 3 enzyme units; reduced glutathione, 50 mM; HMG-CoA (glutaryl-3-^{14}C, New England Nuclear), 0.2 mM (0.1 μCi); and partially purified enzyme stock solution, 100 μL.

Test compounds or compactin (after first being converted to the sodium salt of their dihydroxy acid form in situ by addition of 1 N NaOH (1 equiv)) were added to the assay system in 10-μL volumes at multiconcentration levels. After a 40-min incubation at 37 °C with shaking and exposure to air, the reaction was stopped by the addition of 0.4 mL of 8 N HCl. After an additional 30-min incubation period at 37 °C to ensure the complete lactonization of mevalonic acid to mevalonolactone, 0.2 mL of the mixture was added to an 0.5 × 5.0 cm column containing 100–200-mesh Bio-Rex 5, chloride form (Bio-Rad), wetted with distilled water, as described by Alberts et al.[9] The unreacted [^{14}C]HMG-CoA was absorbed on the resin and the [^{14}C]mevalonolactone was eluted with distilled water (2 × 1 mL) directly into 7-mL scintillation vials. Five milliliters of Aquasol-2 (New England Nuclear) was added to each vial, and radioactivity was measured in a Packard Tri Carb Prias scintillation counter. IC_{50} values were determined by plotting percentage inhibition against test compound concentration and fitting a straight line to the resulting data by using the least-squares method. 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.

Acknowledgment. We are indebted to Drs. R. F. Hirschmann 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.

Registry No. 2, 70017-27-5; (±)-**3**, 93863-41-3; (±)-**4**, 93863-42-4; **5**, 93863-43-5; (±)-**6a**, 86097-37-2; (+)-**6a**, 78444-38-9; (−)-**6a**, 78444-39-0; (±)-**6b**, 86097-38-3; (±)-**7**, 86097-55-4; (±)-**8**, 93863-44-6; (±)-**8** (lactol), 93863-87-7; (±)-**9**, 93922-58-8; (±)-**9** (lactol), 93922-60-2; (±)-**10**, 93863-45-7; (±)-**11**, 93863-46-8; (±)-**12**, 93863-47-9; (±)-**13a**, 93863-48-0; (±)-**13b**, 93863-49-1; (±)-**14**, 93863-50-4; **15**, 93863-51-5; (±)-**16**, 93863-52-6; (±)-**17**, 93863-53-7; **18**, 93863-54-8; (±)-**19**, 93863-55-9; (±)-*erythro*-**20**, 93863-56-0; (±)-*threo*-**20**, 93863-57-1; **21**, 66-77-3; **22**, 13026-12-5; (±)-**23**, 93863-58-2; (±)-**23** (acid chloride), 93863-59-3; (±)-**24**, 93863-60-6; (±)-**25**, 93863-61-7; (±)-**26**, 93863-62-8; (±)-**26** (acid chloride), 93863-63-9; (±)-**27**, 93863-64-0; **28**, 93863-65-1; **29**, 70067-70-8; **30**, 53531-16-1; **31**, 27650-86-8; **32**, 93863-66-2; **33**, 93863-67-3; **34**, 52582-89-5; **35**, 18228-55-2; **36**, 120-83-2; **37**, 17944-27-3; **37** (diethyl acetal), 78830-79-2; **38**, 93863-68-4; **39**, 93863-69-5; **40**, 93863-70-8; **41**, 93863-71-9; (±)-**42**, 93863-72-0; (±)-**43**, 93863-73-1; DL-**44**, 86097-50-9; (±)-**45**, 86097-49-6; (±)-**46**, 93863-74-2; (±)-**47**, 93863-75-3; (±)-**48**, 93863-76-4; (±)-**49**, 93863-77-5; (±)-**50**, 93922-59-9; (±)-**51**, 93863-78-6; (±)-**52**, 93863-79-7; (±)-**53**, 93863-80-0; (±)-**54**, 86118-13-0; (±)-**55**, 93863-81-1; (±)-**55a**, 93863-82-2; (±)-**56**, 93863-83-3; (±)-**57**, 93863-84-4; (±)-**58**, 93863-85-5; $BrCH_2CH(OEt)_2$, 2032-35-1; CH_3CHO, 75-07-0; $CH_3COCH_2CO_2CH_3$, 105-45-3; $CH_2{=}C(OAc)CH_3$, 108-22-5; $CH_2(CO_2H)_2$, 141-82-2; $BrCH_2COBr$, 598-21-0; $BrCH_2CO_2Et$,

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105-36-2; $NCCH_2CO_2H$, 372-09-8; (*Z*)-(*n*-Bu)$_3$SnCH=CHOEt, 64724-29-4; 2,4-dichlorobenzaldehyde, 874-42-0; *N*-((*S*)-α-methylbenzyl)-3(*R*),5(*S*)-dihydroxy-7-(2,4-dichlorophenyl)-6-(*E*)-heptenamide, 93922-56-6; *N*-((*S*)-α-methylbenzyl)-3*S*,5*R*-dihydroxy-7-(2,4-dichlorophenyl)-6-(*E*)-heptenamide, 93922-57-7; 6-(2,4-dichlorophenyl)-3,5-hexadien-2-one, 93863-86-6; diketene, 674-82-8; 4-phenanthrenecarboxaldehyde, 41498-43-5; HMG-CoA reductase, 9028-35-7.

Acyclic Analogues of 2′-Deoxynucleosides Related to 9-[(1,3-Dihydroxy-2-propoxy)methyl]guanine as Potential Antiviral Agents[1,2]

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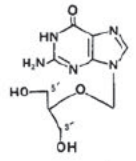
A series of acyclic analogues of 2′-deoxynucleosides related in structure to 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (DHPG, **1**) have been synthesized and evaluated for antiviral activity against herpes simplex virus type 1 (F strain). Additionally, the ability of these analogues to function as substrates for the virus-specified thymidine kinase was examined. Phosphorylation by this kinase is essential for antiviral activity. Although the acyclic 4-oxopyrimidine nucleosides were substrates for the kinase, they were devoid of antiviral activity. In the purine series, most analogues similar in structure to DHPG did exhibit significantly lower antiviral activity, indicating that even small modifications in the purine substituents substantially reduce the antiviral potency. The most active agent, 2,6-diaminopurine **27**, was only poorly phosphorylated by the viral kinase; therefore, its activity was most likely due to a prior enzymatic deamination to give DHPG. Evaluation of **27** in a mouse encephalitis model has shown it to be nearly as potent as DHPG (**1**).

The synthesis of 9-[(1,3-dihyroxy-2-propoxy)methyl]-guanine (DHPG, **1**),[3] a potent antiherpetic agent, was recently reported independently by us[4] and others.[5] DHPG

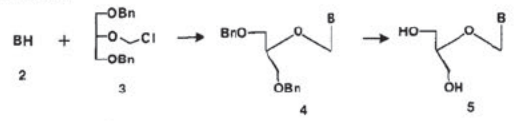


1

is a member of a class of selective antiherpetic nucleoside analogues[6] which includes 9-[(2-hydroxy-1-ethoxy)-methyl]guanine (acyclovir),[7] (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU),[8] and 1-(2-deoxy-2-fluoro-β-D-*arabino*-furanosyl)-5-iodocytosine (FIAC).[9] Of this class, DHPG appears exceptionally promising, being found to be effective against not only herpes simplex virus types 1 and 2[10] but also cytomegalovirus,[10,11a] varicella-zoster,[11b] and Epstein–Barr virus.[11a] The selectivity of these antiviral agents is due in part to the fact that they are appreciably phosphorylated only in virus-infected cells, where a virus-specified thymidine kinase of low substrate specificity converts the nucleoside analogues to 5′-monophosphates. The monophosphates are next converted to diphosphates and then to the corresponding nucleoside triphosphates by cellular enzymes. The triphosphates prevent virus replication by inhibition of the viral DNA polymerase. Additional selectivity is realized at this stage because the host polymerase is less sensitive than the viral polymerase to the nucleoside triphosphate analogue.[6b]

The potent and broad activity of DHPG against herpes viruses prompted us to synthesize other members of this class of acyclic deoxynucleosides. In this report we describe the synthesis of a number of pyrimidine and purine analogues of DHPG, some of which were recently disclosed by Ogilvie and co-workers in a series of publications.[12] This paper details the synthesis of new compounds and our somewhat differing approaches to the recently reported analogues. Additionally, we present new in vitro and in

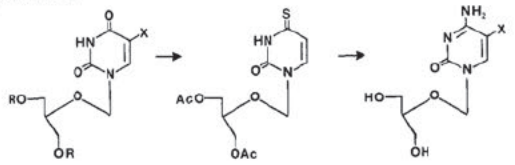
Scheme I



B

a 1-uracilyl
b 1-thyminyl
c 1-(5-fluoro)uracilyl
d 9-(6-chloro)purinyl
e 9-adeninyl
f 9-hypoxanthinyl

Scheme II



6 X=H, R=Ac
9 X=F, R=Ac
11 X=Br, R=Ac
12 X=Br, R=H

7

8 X=H
10 X=F

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(2) Presented in part at the 185th National Meeting of the American Chemical Society, Seattle, WA; CARB 43; March 24, 1983.
(3) The structural formulas of DHPG (**1**) and the related acyclic nucleoside analogues have been depicted in a "ribose-like" conformation only to draw attention to the similarity in structure between these compounds and 2′-deoxynucleosides. In accordance with this representation, the two terminal carbons of the glycerol are referred to as the 3′- and 5′-positions.

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