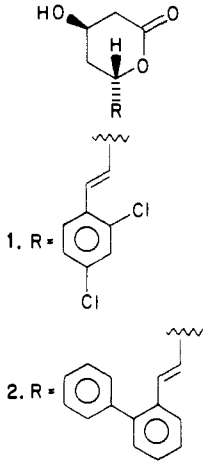
3-Hydroxy-3-methylglutaryl-coenzyme A Reductase Inhibitors. 3. 7-(3,5-Disubstituted [1,1'-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic Acids and Their Lactone Derivatives

G. E. Stokker,*† A. W. Alberts,‡ P. S. Anderson,† E. J. Cragoe, Jr.,† A. A. Deana,† J. L. Gilfillan,‡ J. Hirshfield,‡ W. J. Holtz,† W. F. Hoffman,† J. W. Huff,‡ T. J. Lee,† F. C. Novello,† J. D. Prugh,† C. S. Rooney,† R. L. Smith,† and A. K. Willard†,§

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, and Rahway, New Jersey 07065.
Received May 2, 1985

The syntheses of a series of 7-(3,5-disubstituted [1,1'-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acids and their lactones are reported. Intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitory activity is enhanced markedly when the biphenyl moiety is substituted by chloro or methyl groups at positions 3 and 5 and a fluoro group at position 4'. These substitutions, followed by resolution, provided compounds **100**(+) and **110**(+) with 2.8 times the intrinsic inhibitory activity of compactin. Compound **100**(+) was shown to possess the same chirality in the lactone ring as compactin by single-crystal X-ray crystallography.

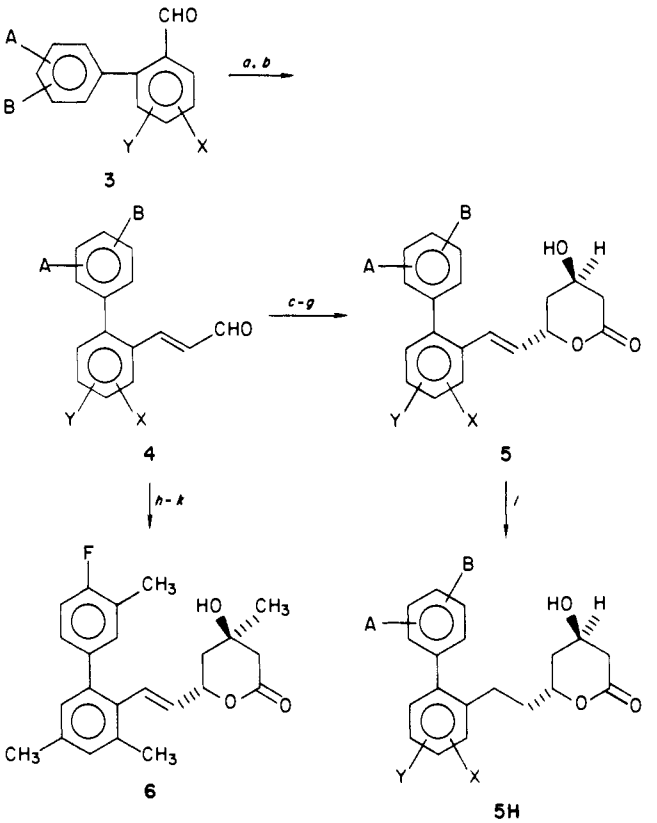
We previously reported on a series of 3,5-dihydroxypentanoic acids, their δ lactones, and other derivatives which were shown to possess varying degrees of intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity.[1] The most potent inhibitor bearing a monocyclic substituent was the dihydroxy acid form of lactone **1**. In part 2, we described the structure–activity relationships (SAR) determined for a series of 7-phenyl-3,5-dihydroxy-6-heptenoic (and heptanoic) acids bearing different aryl substituents.[2] Lactone **2** emerged as the most interesting monosubstituted phenyl compound of this series and potentially the most exploitable. In the



present study, we have extended the latter investigation by determining the effects of aryl substitution on both rings of a series of 7-(3,5-disubstituted [1,1'-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acids on activity. Use of the 3,5-disubstitution pattern in the biphenyl moiety was based on the observations of part 2 wherein the 2,4,6-trisubstitution pattern on the phenyl ring was shown to be optimal. This report also extends the investigation of bridging elements between the two aryl rings with a direct bond, a methylene, ethylene, or ethenyl unit. The other bridges previously examined were oxygen, methyleneoxy, and oxymethylene.[2]

Chemistry. The compounds prepared for this study are listed in Table III and their syntheses are summarized in Schemes I–IV. With the exception of **6**, all of the

Scheme I



[a] *n*-$Bu_3SnCH{=}CHOEt$, *n*-BuLi. [b] H_3O^+. [c] $^-CH_2CO^-CHCO_2CH_3$. [d] $NaBH_4$. [e] OH^-. [f] H^+. [g] $C_6H_5CH_3$, Δ. [h] *n*-Bu_3SnOCH_3, $CH_2{=}C(OAc)CH_3$. [i] HO_2CCO_2H. [j] $BrCH_2COBr$, C_5H_5N. [k] Zn, CuBr, Et_2AlCl. [l] H_2, Rh/C.

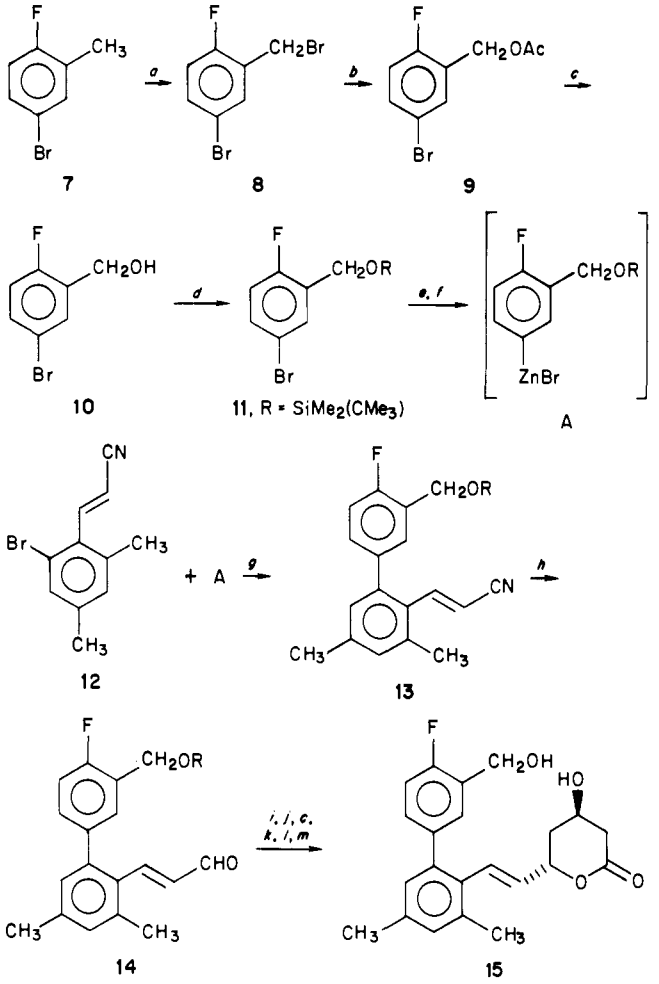
6-substituted 4-hydroxypyran-2-ones were synthesized from the appropriate aldehydes via condensation with the dianion of methyl acetoacetate followed by borohydride reduction, hydrolysis, and lactonization as described in part 1. The characterization of the trans isomer was based on the chemical shift of the C-6 and the coupling constants

† Merck Sharp & Dohme, West Point, PA.
‡ Merck Sharp & Dohme, Rahway, NJ.
§ Present address: Stuart Pharmaceuticals, Division of ICI Americas, Wilmington, DE 19897.

(1) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
(2) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan, J. L.; Gould, N. P.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Rittle, K. E.; Smith, R. L.; Stokker, G. E.; Willard, A. K. *J. Med. Chem.*, preceding paper in this issue.

0022-2623/86/1829-0170$01.50/0

Scheme II



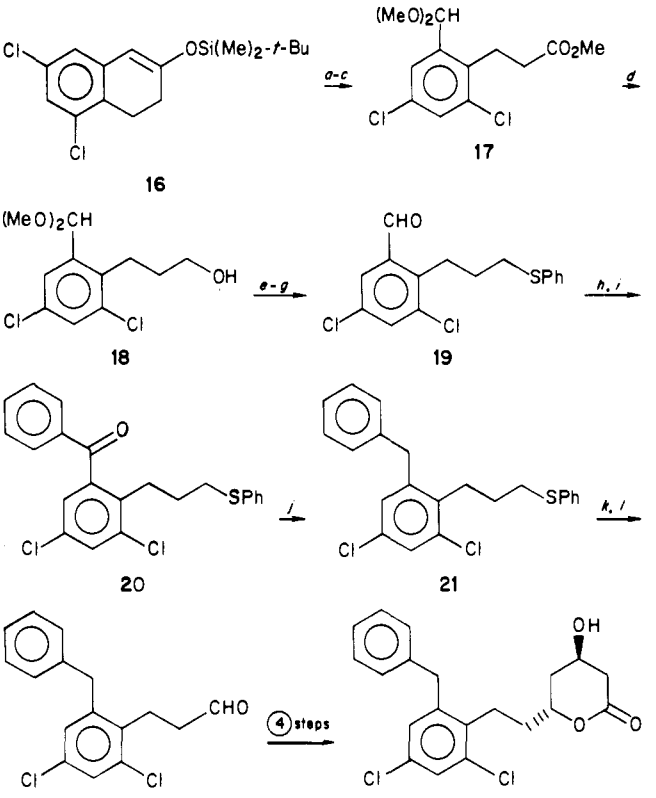
[a] Br_2, $h\nu$. [b] NaOAc, Δ. [c] OH^-. [d] $ClSi(CH_3)_2C(CH_3)_3$. [e] Mg. [f] $ZnBr_2$. [g] $Ni(Ph_3P)_2Cl_2$. [h] Dibal. [i] $^-CH_2CO^-CHCO_2CH_3$. [f] Et_3B, $NaBH_4$, −98 °C. [k] H^+. [l] $C_6H_5CH_3$, Δ. [m] $(n\text{-}C_4H_9)_4NF$.

of the C-4 protons in the NMR as described in part 2.[2] (Since the completion of the work described in part 1, a trialkylborane-mediated stereoselective reduction of β-hydroxy ketones has been described.[3] This reduction yields a much higher percentage of the desired erythro diol and an illustrative example (**15a**) is included in the experimental section.) The *cis*-6-ethenyl-4-hydroxypyran-2-ones (i.e., the biologically inactive isomers) may be epimerized at C_6 to a 1:1 (cis–trans) mixture by refluxing in aqueous acetonitrile with 1 equiv of mercuric chloride. The resolution of lactones **100** and **110** was accomplished via chromatographic separation of their respective diastereomeric (*S*)-α-methylbenzylamides followed by basic hydrolysis and relactonization to yield **100(+)**, **100(−)**, **110(+)**, and **110(−)**. Lactone **6** was prepared by an intramolecular Reformatsky reaction of the antecedent 4-(2-bromoacetoxy)-6-hexen-2-one which was obtained after bromoacylation of the aldol product of acetone and propenal **84** (Scheme I).

The synthesis of biphenylylpropenals **4** (Table II) was accomplished by condensation of the corresponding biphenylcarboxaldehyde (**3**) with lithium ethoxyethylene (Scheme I) as described in part 1 with the exception of **14**. In the latter instance, conversion of 4-bromo-2-methyl-1-fluorobenzene (**7**) to silyl ether **11** was effected via the

(3) Narasaka, K.; Pai, F. C. *Tetrahedron Lett.* **1984**, *40*, 2233.

Scheme III



[a] O_3. [b] Me_2S. [c] MeOH, H^+. [d] LAH. [e] TosCl, py. [f] C_6H_5SNa. [g] H_3^+O. [h] C_6H_5MgBr. [i] Me_2SO, TFAA then Et_3N. [j] NH_2NH_2, KOH. [k] NCS. [l] Cu^{2+}.

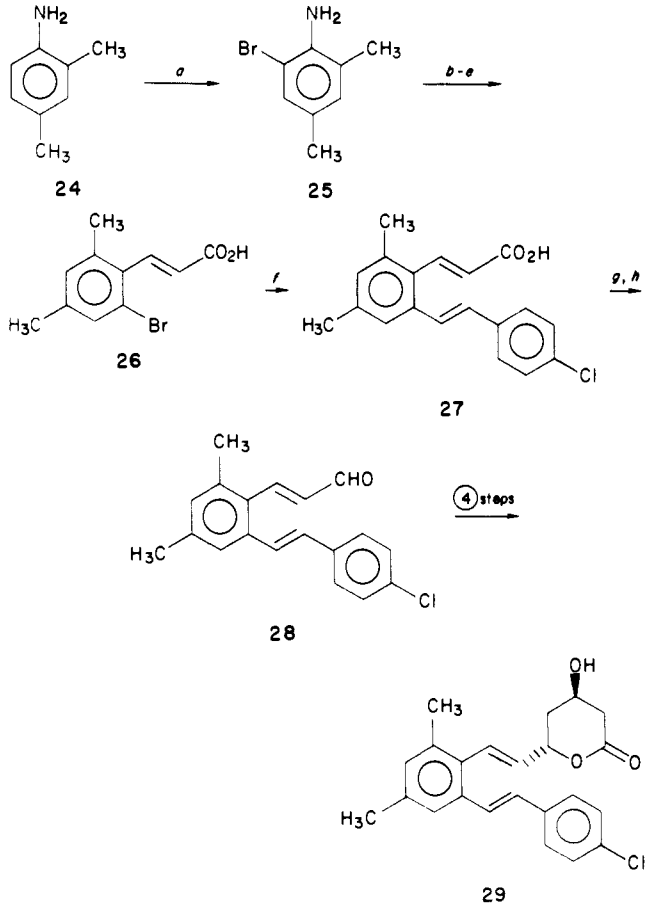
four-step sequence **7** → **8** → **9** → **10** → **11**, using the reagents indicated in Scheme II. Grignard formation followed by transmetalation with anhydrous zinc bromide provided arylzinc bromide A, which was immediately coupled with cinnamyl nitrile **12** catalyzed by bis(triphenylphosphine)nickel dichloride.[4] Reduction of nitrile **13** with diisobutylaluminum hydride (Dibal) provided aldehyde **14**, the requisite biphenylylpropenal for lactone **15**. The elaboration of the only non biphenyl aldehydes (**22** and **28**) required for the dianion condensation route are outlined in Schemes III and IV, respectively.

Ozonolysis of **16** followed by reductive workup and subsequent acid methanolysis provided **17**, which was reduced to propanol **18**. Conversion of **18** to the corresponding tosylate followed by displacement by thiophenoxide and then acid hydrolysis yielded **19**. Grignard addition of phenylmagnesium bromide to aldehyde **19** followed by Swern oxidation gave benzophenone **20**, which was then subjected to a Wolff–Kishner reduction (**21**) and a halogen-mediated oxidation to form **22**.

Scheme IV delineates the preparation of propenal **28** from aniline **24**. Meerwein arylation of methyl acrylate with the diazonium salt of **25** followed by treatment with potassium hydroxide at elevated temperature provided **26**. Treatment of **26** with 4-chlorostyrene under Heck[5] arylation conditions yielded cinnamic acid **27**, which was then converted to **28** via its acid chloride by reduction with bis(triphenylphosphine)copper(I) tetrahydroborate.[6]

(4) Sletzinger, M.; Verhoven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M. H. *Tetrahedron Lett.* **1985**, 2951.
(5) Plevyak, J. E.; Dickenson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.
(6) Fleet, G. W. J.; Fuller, C. J.; Harding, P. J. C. *Tetrahedron Lett.* **1978**, 1440.

Scheme IV

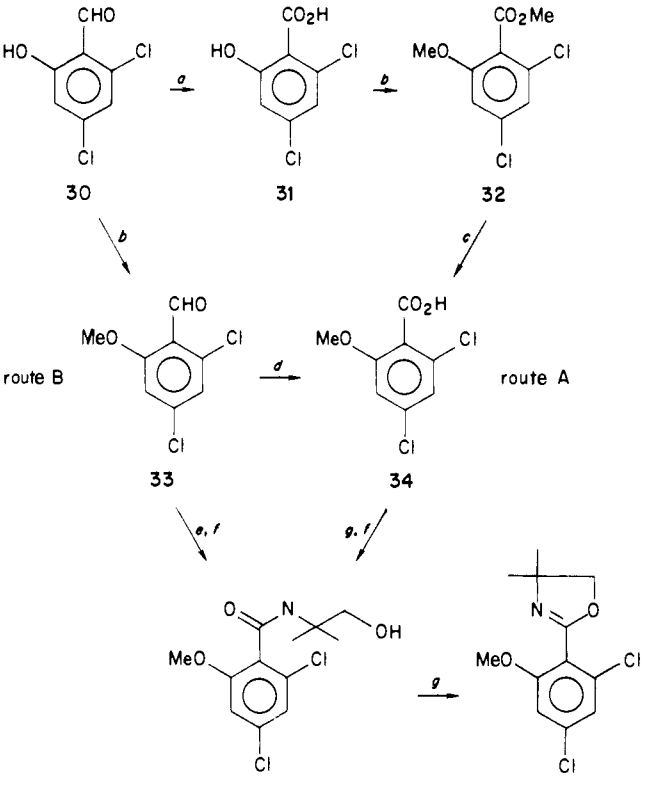


[a] Br_2. [b] HONO. [c] $CH_2=CHCO_2Et$. [d] OH^-, Δ. [e] H_3^+O. [f] 4-Cl-$C_6H_4CH=CH_2$, $(C_6H_5)_3P$, $Pd(OAc)_2$, 1 mol %, Et_3N, Δ. [g] $SOCl_2$. [h] $((C_6H_5)_3P)_2CuBH_4$, $(C_6H_5)_3P$.

The biphenylcarboxaldehydes **3** (Table I) were prepared by the two independent methods summarized in Schemes V and VI (method 1) and Scheme VII (method 2). Method 1, the key step of which is based on the work of Meyers,[7] involves an aryl-Grignard displacement of the 2-methoxy group of **36** followed by quaternization with methyl iodide, borohydride reduction, and acidic hydrolysis.[8] No product resulting from displacement of the 6-chloro group was detected in the Grignard reaction on **36**. The apparent inactivity of the *o*-chloro substituent in this displacement was confirmed by failure to detect any biphenylyloxazoline in the reaction of phenylmagnesium bromide with 2-(2,6-dichlorophenyl)-4,5-dihydro-4,4-dimethyloxazole under identical conditions. The synthesis of **35**, the immediate precursor to **36**, is outlined in Scheme V. In the original route (A), **30** → **31** → **32** → **34** → **35**, only the demethylation of **32** requires comment. The nucleophilic displacement of sterically hindered carboxylates by tertiary amines (DBN,[9] Dabco,[9] 3-quinnuclidinol,[9] and 1,1-dimethylhydrazine[10]) is well-known. The use of 4-(aminomethyl)piperidine as the nucleophile allowed a lower temperature (100 °C vs. 140 °C for the bicyclic amines) and a shorter reaction time ($1^1/_2$ h vs. 6–12 h for the hydrazine) to be used, and although of no real advantage in this instance, 4-(aminomethyl)piperidine was found to be superior to the other amines studied for this transformation (i.e., *N*-methylbenzylamine, 2,6-dimethylmorpholine, piperidine, 2,6-dimethylpiperidine, or 2-amino-2-methyl-1-propanol). Proton and ^{13}C NMR examination of the amine recovered after displacement showed that only the secondary amine was methylated, and when 2-amino-2-methyl-1-propanol was used, the only methylated amine detected was the (*N*,*N*-dimethylamino)propanol.

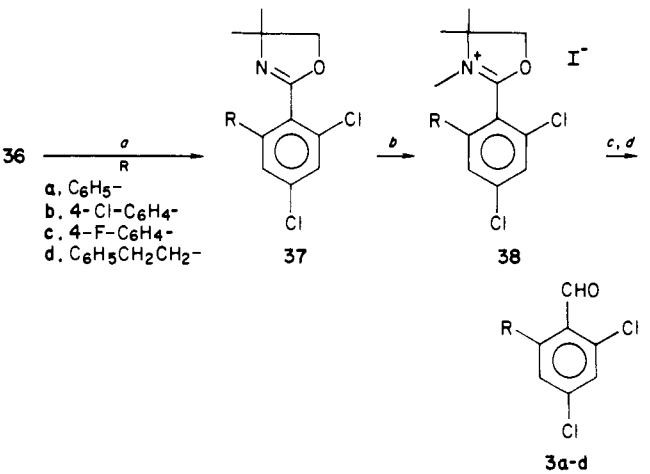
Route B, the more expeditious of the two routes, was based on the key conversion of **33** → **35** via radical bromination/oxidation and subsequent amination.[11] The oxidation of **33** → **34** with "purple benzene", essentially

Scheme V. Method 1



[a] Ag_2O. [b] MeI, K_2CO_3, DMF. [c] 4-NH_2CH_2-c-$C_5H_{10}N$, Δ. [d] *n*-Bu_4NI, $KMnO_4$, C_6H_6, H_2O. [e] NBS, *hν*. [f] $H_2NC(CH_3)_2CH_2OH$. [g] $SOCl_2$.

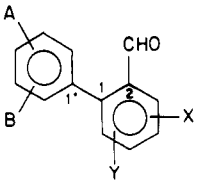
Scheme VI. Method 1



[a] RMgX. [b] MeI. [c] $NaBH_4$. [d] H_3O^+, Δ.

(7) Meyers, A. I.; Gabel, R.; Mihelich, E. *J. Org. Chem.* **1978**, *43*, 1372.
(8) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531.
(9) Miles, D. H.; Huang, B.-S. *J. Org. Chem.* **1976**, *41*, 208 and references cited therein.
(10) Kasina, S.; Nematallahi, J. *Tetrahedron Lett.* **1978**, 1403.
(11) Cheung, Y.-F. *Tetrahedron Lett.* **1979**, 3809

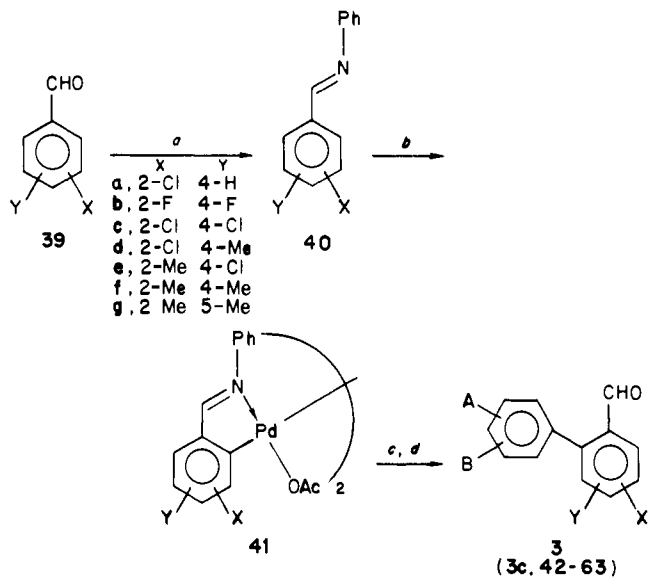
Table I. Physical Properties of Biphenylcarboxaldehydes 3[a]



no.	A	B	X	Y	method	recryst solvent	yield,[b] %	mp, °C	formula	anal.[c,d]
3d	H	H	3-Cl	5-Cl	1	pet. ether	80	48–50	$C_{13}H_8Cl_2O$	C, H
3d[e]	H	H	3-Cl	5-Cl	1	*n*-BuCl/hexane	45	82–83.5	$C_{15}H_{12}Cl_2O$	C, H[f]
42	2′-Me	H	3-Cl	5-Cl	2		70	oil	$C_{14}H_{10}Cl_2O$	*g*
43	3′-Me	H	3-Cl	5-Cl	2	hexane	75	84–85	$C_{14}H_{10}Cl_2O$	C, H
44	4′-Me	H	3-Cl	5-Cl	2		61	oil	$C_{14}H_{10}Cl_2O$	*g*
45[h]	3′-Et	H	3-Cl	5-Cl	2		68	oil	$C_{15}H_{12}Cl_2O$	*g*
46	3′-MeO	H	3-Cl	5-Cl	2	CH_2Cl_2/hexane	58	97–98	$C_{14}H_{10}Cl_2O_2$	C, H
47	4′-MeO	H	3-Cl	5-Cl	2	hexane	64	90–91.5	$C_{14}H_{10}Cl_2O_2$	C, H
3b	4′-Cl	H	3-Cl	5-Cl	1		23	89–92	$C_{13}H_{17}Cl_3O$	*g*
48	3′-F	H	3-Cl	5-Cl	2		67	gum	$C_{13}H_7Cl_2FO$	*g*
3c	4′-F	H	3-Cl	5-Cl	1	pet. ether	64 (37)[i]	73–74	$C_{13}H_7Cl_2FO$	C, H
					2	pet. ether	73 (72)[i]	71–73		
49	4′-F	H	3-F	5-F	2		59	69–71	$C_{13}H_7F_3O$	*g*
50	4′-F	H	3-Me	5-Me	2	hexane	74	68–70	$C_{15}H_{13}FO$	C, H
51	3′-Me	5′-Me	3-Cl	5-Cl	2	hexane	79	103–105	$C_{15}H_{12}Cl_2O$	C, H
52	3′-Me	5′-Me	3-Me	5-Me	2	sublimed	85	79–81	$C_{17}H_{18}O$	C, H
53	2′-Me	4′-F	3-Cl	5-Cl	2		64	gum	$C_{14}H_9Cl_2FO$	*g*
54	3′-Me	4′-F	3-Cl	H	2	CH_2CL_2/hexane	71	74–79	$C_{14}H_{10}ClFO$	C, H
55	3′-Me	4′-F	3-Cl	5-Me	2	CH_2Cl_2/hexane	66	70–73	$C_{15}H_{12}ClFO$	C, H
56	3′-Me	4′-F	3-Me	5-Cl	2		49	sticky solid	$C_{15}H_{12}ClFO$	*g*
57	3′-Me	4′-F	3-Cl	5-Cl	2	hexane	64	77–79	$C_{14}H_9Cl_2FO$	C, H
58	3′-Me	4′-F	3-Me	5-Me	2	sublimed	82	80–81	$C_{16}H_{15}FO$	C, H
59[j]	3′,5′-Me_2	4′-F	3-Me	5-Me	2	sublimed	76	137–139	$C_{17}H_{17}FO$	C, H
60	3′-Cl	4′-Cl	3-Cl	5-Cl	2	hexane	83	118–119	$C_{13}H_6Cl_4O$	C, H
61	3′-Cl	5′-Cl	3-Cl	5-Cl	2	hexane	75	106–106.5	$C_{13}H_6Cl_4O$	C, H
62	3′-Cl	4′-Cl	3-Me	5-Me	2	hexane	75	80–81	$C_{15}H_{12}Cl_2O$	C, H
63	3′-Cl	4′-Cl	3-Me	6-Me	2		36	gum	$C_{15}H_{12}Cl_2O$	*g*

[a] All of the starting benzaldehydes (**30** or **39**) were commercially available as were the bromides for the Grignard reaction unless so indicated. [b] Represents overall yield from Grignard reaction. [c] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [d] ^1H NMR spectra were recorded on all compounds in $CDCl_3$ and the diagnostic aldehydic proton appeared as a singlet between δ 9.9 and 10.3. Complete spectra are available as supplementary material. [e] Ethyl bridge between aryl rings. [f] Anal. Calcd: C, 64.54. Found: C, 63.76. [g] This compound was isolated but not purified or analyzed before use in next step. [h] Pope, G. W.; Bogert, M. T. *J. Org. Chem.* **1937**, *2*, 276. [i] Represents overall yield from starting benzaldehydes **30** or **39c**. [j] See Experimental Section (**59a**).

Scheme VII. Method 2



[a] $H_2NC_6H_5$. [b] $Pd(OAc)_2$. [c] ABC_6H_3MgX, 4 equiv of Ph_3P. [d] H_3^+O.

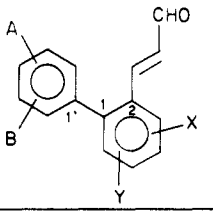
combining routes A and B, was tried because the oxidation of **33** with basic Ag_2O was unsuccessful.

A more facile procedure for the preparation of **3** is shown in Scheme VII (method 2). This three-step palladium-mediated sequence is based on that of Murahashi.[12] Four equivalents of triphenylphosphine per atom of palladium was required whenever there was a reducible halogen (Cl) because, with lesser amounts of the phosphine (i.e., only 3 equiv in the preparation of **47** or **48**), all of the possible monochloro isomers were also isolated. In addition to the deschloro byproducts isolated in the synthesis of **47**, the corresponding symmetrical biphenyl (a ubiquitous byproduct in the formation of stabilized aryl-Grignard reagents, a phenomenon unrelated to this particular reaction) was isolated along with 1,1-bis(4-methoxyphenyl)ethylene. The formation of the latter was interpreted to result from a 2-fold addition of the Grignard reagent to the acetate ligand of the Pd(II) complex followed by dehydration. This byproduct can be obviated by using the Pd(II) complex wherein the acetate ligand is replaced by chloride.

X-ray Crystallography. The absolute configuration of the more potent, dextrarotatory enantiomer of translactone **100(±)** was determined by X-ray crystallographic analysis. This enantiomer was found to have 4*R*,6*S* chirality in the lactone portion corresponding to the analogous centers in compactin or mevinolin; the conformation is illustrated in Figure 1. The dihedral angle between the two aryl rings (atoms C_{11}, C_{10}, C_{15}, and C_{16}) is 54.7° and

(12) Murahashi, S.; Tamba, Y.; Yamamura, M.; Yoshimure, N. *J. Org. Chem.* **1978**, *43*, 4099.

Table II. Physical Properties of 3-Biphenylylpropenals 4



no.	A	B	X	Y	recryst solvent	yield, %	mp, °C	formula	anal.[a,b]
64	H	H	3-Cl	5-Cl	hexane	83	76–77	$C_{15}H_{10}Cl_2O$	C, H
65[c]	H	H	3-Cl	5-Cl		66	gum	$C_{17}H_{14}Cl_2O$	*d*
66	2′-Me	H	3-Cl	5-Cl	hexane	47	98–99	$C_{16}H_{12}Cl_2O$	C, H
67	3′-Me	H	3-Cl	5-Cl		67	oil	$C_{16}H_{12}Cl_2O$	*d*
68	4′-Me	H	3-Cl	5-Cl	hexane	67	109–111	$C_{16}H_{12}Cl_2O$	C, H
69	3′-Et	H	3-Cl	5-Cl		79	oil	$C_{17}H_{14}Cl_2O$	*d*
70	3′-MeO	H	3-Cl	5-Cl	Et_2O	63	81–82	$C_{16}H_{12}Cl_2O_2$	C, H
71	4′-MeO	H	3-Cl	5-Cl	hexane	63	94–95	$C_{16}H_{12}Cl_2O_2$	C, H
72	4′-Cl	H	3-Cl	5-Cl	toluene/hexane	64	96–97.5	$C_{15}H_9Cl_3O$	C, H
73	3′-F	H	3-Cl	5-Cl	hexane	71	91–92	$C_{15}H_9Cl_2FO$	C, H[e]
74	4′-F	H	3-Cl	5-Cl	toluene/hexane	64	136–138	$C_{15}H_9Cl_2FO$	C, H
75	4′-F	H	3-F	5-F	hexane	69	81–82	$C_{15}H_9F_3O$	C, H
76	4′-F	H	3-Me	5-Me	pet. ether	81	70–72	$C_{17}H_{15}FO$	C, H
77	3′-Me	5′-Me	3-Cl	5-Cl		66	oil	$C_{17}H_{14}Cl_2O$	*d*
78	3′-Me	5′-Me	3-Me	5-Me	sublimed	74	gum	$C_{19}H_{20}O$	*d*
79	2′-Me	4′-F	3-Cl	5-Cl		61	gum	$C_{16}H_{11}Cl_2FO$	*d*
80	3′-Me	4′-F	3-Cl	H		37	oil	$C_{16}H_{12}ClFO$	*d*
81	3′-Me	4′-F	3-Cl	5-Me		60	79–81	$C_{17}H_{14}ClFO$	C, H[f]
82	3′-Me	4′-F	3-Me	5-Cl		40	oil	$C_{17}H_{14}ClFO$	*d*
83	3′-Me	4′-F	3-Cl	5-Cl	hexane	84	98.5–99.5	$C_{16}H_{11}Cl_2FO$	C, H
84	3′-Me	4′-F	3-Me	5-Me	sublimed	49	82–84	$C_{18}H_{17}FO$	C, H
85	3′,5′-Me_2	4′-F	3-Me	5-Me	sublimed	70	78–80	$C_{19}H_{19}FO$	C, H
86	3′-Cl	4′-Cl	3-Cl	5-Cl		59	gum	$C_{15}H_8Cl_4O$	*d*
87	3′-Cl	5′-Cl	3-Cl	5-Cl		49	gum	$C_{15}H_8Cl_4O$	*d*
88	3′-Cl	4′-Cl	3-Me	5-Me		66	gum	$C_{17}H_{14}Cl_2O$	*d*
89	3′-Cl	4′-Cl	3-Me	6-Me		58	gum	$C_{17}H_{14}Cl_2O$	*d*

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] ^1H NMR spectra were recorded on all compounds in $CDCl_3$ and the chemical shifts for the aldehydic and α-vinyl protons were δ 9.5–9.65 (d, J = 7.0–7.5 Hz) and 6.2–6.4 (dd, J = 15.0–16.0 and 7.0–7.5 Hz), respectively. Complete spectra are available as supplementary material. [c] Ethyl bridge between aryl rings. [d] This compound was isolated but not purified or analyzed before use in next step. [e] Anal. Calcd: C, 61.04. Found: C, 61.47. [f] Anal. Calcd: H, 4.84. Found: H, 5.36.

that between the central aryl ring and the ethylene bridge (atoms C_7, C_8, C_9, and C_{10}) is 57.5°.

Biological Results and Discussion

The target compounds presented in Table III were tested as the ring-opened dihydroxy carboxylate forms for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase. The study of nuclear substitution on the central phenyl ring of the biphenyl moiety was confined to that of methyl or chloro in the 3- and 5-positions. Inhibitory potency increased by greater than 40-fold when chloro groups were introduced concomitantly in the 3- and 5-positions (**90** vs. **2**). The potency of the 3-chloro compound (**106**) was less than half that of the 3,5-dichloro compound (**109**). Replacement of the 5-chloro group in **109** by a methyl group (**107**) resulted in a slight reduction in potency, while transposition of these two groups (**107** → **108**) increased the potency by 2.3-fold. In some cases, the replacement of both chloro groups by methyl groups resulted in a modest diminution of potency (**100** vs. **102** and **103** vs. **104**), while in others a substantial increase in potency was observed (**109** vs. **110** and **112** vs. **114**). Replacement of the two chloro groups in compound **100** with fluoro groups (**101**) resulted in a marked loss of potency. Movement of the methyl from position 5 (**114**) to position 6 (**115**) resulted in a moderate loss of potency.

Type and position of substituents on the external phenyl ring were more critical. An electron-donating group in the 4′-position (i.e., CH_3 in **94** or CH_3O in **97**) was detrimental when compared to H (**90**), whereas a halogen in this position was beneficial (i.e., Cl in **98** or F in **100**). A methyl in the 2′-position was also contraindicated (**92** vs. **90**, **105** vs. **100**, and **105** vs. **109**). An electron-donating group at the 3′-position may increase potency (CH_3 in **93** vs. **90** and

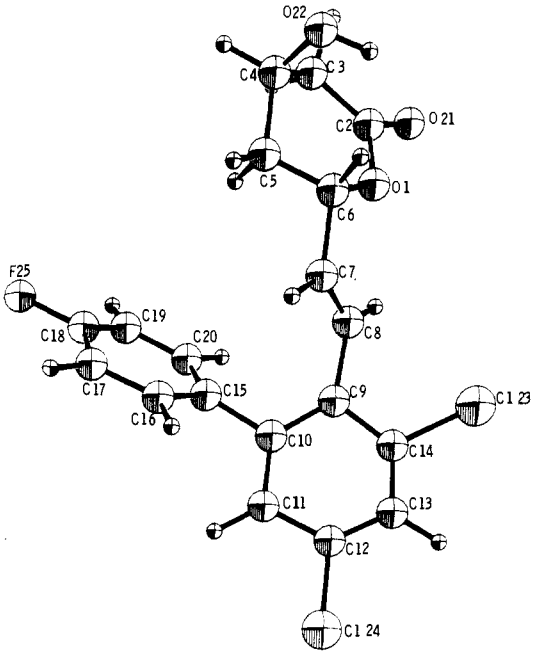
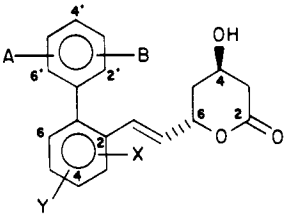


Figure 1. Computer-generated ORTEP drawing of one formula unit of structure **100**(+) within the unit cell.

Table III. Physical Properties and in Vitro HMG CoA Reductase Inhibitory Activities of Lactones **5** and **6**



no.	A	B	X	Y	recryst solvent	mp, °C	formula[a]	IC_{50}, μM	rel potency[b]
1			3-Cl	5-Cl	acetone/hexane	147–149	$C_{13}H_{12}Cl_2O_3$	21.9	0.06
2	H	H	H	H	Et_2O	90–92	$C_{19}H_{18}O_3$	3.0	0.63
2H[c]	H	H	H	H		oil	$C_{19}H_{20}O_3$	44	0.04
6[d]	3′-Me	4′-F	3-Me	5-Me		glass	$C_{23}H_{25}FO_3$	0.106	14
15	3′-CH_2OH	4′-F	3-Me	5-Me	*n*-BuCl	137–138	$C_{22}H_{23}FO_4$	0.049	26.5
23[e]	H	H	3-Cl	5-Cl	Et_2O/hexane	109–110	$C_{20}H_{20}Cl_2O_3$	0.53	4.3
29[f]	4′-Cl	H	3-Me	5-Me	*n*-BuCl	153–153.5	$C_{23}H_{23}ClO_3$	0.63	2.4
90	H	H	3-Cl	5-Cl	*n*-BuCl/hexane	113–115	$C_{19}H_{16}Cl_2O_3$	0.08	26
90H[c]	H	H	3-Cl	5-Cl	$CHCl_3$/hexane	151.5–152	$C_{19}H_{18}Cl_2O_3$	0.1	18
91[g]	H	H	3-Cl	5-Cl	*n*-BuCl	118–119	$C_{21}H_{20}Cl_2O_3$	0.43	2.8
92	2′-Me	H	3-Cl	5-Cl	Et_2O/hexane	140–141	$C_{20}H_{18}Cl_2O_3$	0.37	3.2
93	3′-Me	H	3-Cl	5-Cl		glass	$C_{20}H_{18}Cl_2O_3 \cdot 0.05CHCl_3$	0.016	94
94	4′-Me	H	3-Cl	5-Cl	*n*-BuCl/hexane	119–119.5	$C_{20}H_{18}Cl_2O_3$	0.19	11
95	3′-Et	H	3-Cl	5-Cl		gum	$C_{21}H_{20}Cl_2O_3 \cdot 0.05CHCl_3$	0.044	30
96	3′-MeO	H	3-Cl	5-Cl	Et_2O/hexane	93–94	$C_{20}H_{18}Cl_2O_4$	0.05	26
97	4′-MeO	H	3-Cl	5-Cl	*n*-BuCl/hexane	100–102	$C_{20}H_{18}Cl_2O_4$	0.47	2.6
98	4′-Cl	H	3-Cl	5-Cl	*n*-BuCl/hexane	116.5–118	$C_{19}H_{15}Cl_3O_3$	0.036	58
99	3′-F	H	3-Cl	5-Cl	*n*-BuCl/hexane	130–132	$C_{19}H_{15}Cl_2FO_3$	0.07	38.6
100	4′-F	H	3-Cl	5-Cl	*n*-BuCl/hexane	153–154	$C_{19}H_{15}Cl_2FO_3$	0.024	100
100(+)[h]	4′-F	H	3-Cl	5-Cl	*n*-BuCl/hexane	108–109.5	$C_{19}H_{15}Cl_2FO_3$	0.005	280
100(−)[i]	4′-F	H	3-Cl	5-Cl	*n*-BuCl/hexane	130–131	$C_{19}H_{15}Cl_2FO_3$	0.26	5[j]
101	4′-F	H	3-F	5-F		glass	$C_{19}H_{15}F_3O_3$	0.86	3.5
102	4′-F	H	3-Me	5-Me	CH_2Cl_2/hexane	154–156	$C_{21}H_{21}FO_3$	0.013	96
103	3′-Me	5′-Me	3-Cl	5-Cl		glass	$C_{21}H_{20}Cl_2O_3 \cdot 0.05CHCl_3$	0.013	115
104	3′-Me	5′-Me	3-Me	5-Me	hexane	109–110	$C_{23}H_{26}O_3$	0.015	80
105	2′-Me	4′-F	3-Cl	5-Cl		glass	$C_{20}H_{17}Cl_2FO_3$	0.036	33
106	3′-Me	4′-F	3-Cl	H		140–145	$C_{20}H_{18}ClFO_3$[k]	0.03	40
107	3′-Me	4′-F	3-Cl	5-Me		glass	$C_{21}H_{20}ClFO_3$[l]	0.013	92
108	3′-Me	4′-F	3-Me	5-Cl	Et_2O/hexane	109–110	$C_{21}H_{20}ClFO_3$	0.006	233
109	3′-Me	4′-F	3-Cl	5-Cl		glass	$C_{20}H_{17}Cl_2FO_3 \cdot 0.1CHCl_3$	0.029	100
110	3′-Me	4′-F	3-Me	5-Me	*n*-BuCl/hexane	115–116	$C_{22}H_{23}FO_3$	0.007	171
110(+)[m]	3′-Me	4′-F	3-Me	5-Me	Et_2O/hexane	87–89	$C_{22}H_{23}FO_3$	0.0076	289
110(−)[n]	3′-Me	4′-F	3-Me	5-Me	Et_2O/hexane	86–88	$C_{22}H_{23}FO_3$	7.3	0.18[j]
110H[c]	3′-Me	4′-F	3-Me	5-Me	*n*-BuCl	131.5–133	$C_{22}H_{25}FO_3$[o]	0.022	45
111	3′,5′-Me_2	4′-F	3-Me	5-Me	CH_2Cl_2/hexane	142–146	$C_{23}H_{25}FO_3$	0.01	150
112	3′-Cl	4′-Cl	3-Cl	5-Cl		glass	$C_{19}H_{14}Cl_4O_3$	0.025	116
113	3′-Cl	5′-Cl	3-Cl	5-Cl		glass	$C_{19}H_{14}Cl_4O_3$	0.037	78
114	3′-Cl	4′-Cl	3-Me	5-Me	*n*-BuCl	128–129	$C_{21}H_{20}Cl_2O_3$	0.008	175
115	3′-Cl	4′-Cl	3-Me	6-Me		glass	$C_{21}H_{20}Cl_2O_3$	0.013	123

[a] Analytical results are within ±0.4% of the theoretical values unless otherwise noted. [b] Potency of compactin arbitrarily assigned a value of 100; see part I for full description of protocol. [c] Saturated bridge between biphenyl and lactone moieties. [d] 4-Methyl in lactone ring. [e] Methylene bridge between aryl rings (from **22**). [f] Ethylene bridge between aryl rings (from **28**). [g] Ethyl bridge between aryl rings (from **3d**). [h] $[\alpha]^{20}_D$ +38.80 ($CHCl_3$). [i] $[\alpha]^{20}_D$ −39.85 ($CHCl_3$). [j] Each enantiomer was found to be free of the other enantiomer within the limits of detection (threshold = ca. 2%). Therefore, the activity displayed by the (−) enantiomer was probably due to trace amounts of the (+) enantiomer. [k] Exact mass, calcd *m/e* 360.81; found *m/e* 360.089. [l] Exact mass, calcd *m/e* 374.83; found *m/e* 374.1093. [m] $[\alpha]^{25}_D$ +39.3 ($CHCl_3$); +36.0 (CH_3OH). [n] $[\alpha]^{25}_D$ −35.8 (CH_3OH). [o] Anal. Calcd: C, 74.13. Found: C, 73.56.

110 vs. **102**) or have no effect (CH_3 in **109** vs. **100** or CH_3O in **96** vs. **90** and C_2H_5 in **95** vs. **90**). The later case demonstrated that homologation of the 3′-methyl group attenuated potency (**95** vs. **93**) as did oxidation to the alcohol (**15** vs. **110**). The addition of a halogen at the 3′-position potentiated potency but not as effectively as when introduced at the 4′-position (**99** vs. **100** or **112** vs. **98** vs. **90** and **113** vs. **112**).

The type of bridging between the phenyl rings also proved to be important. When the direct bond in compound **90** was replaced by oxygen, methyleneoxy, or oxymethylene, the potency was decreased by 18-, 7- and 4-fold, respectively.[2] Insertion of a methylene unit between the phenyl rings caused a 4-fold reduction in potency (**23** vs. **90H**), while insertion of an ethylene unit caused a 10-fold reduction (**91** vs. **90**). Although no direct comparison between an ethenyl bridge (**29**) and a direct bond could be made because the corresponding biphenyl was not prepared, the likelihood that the latter would be less potent than compound **29** can be inferred. The replacement of chloro groups in the central phenyl ring by methyls produced a change in potency by a factor between 0.7 and 1.7 (vida supra). Therefore, the 20-fold decrease in potency between **29** and **98** must, in a large part, be due to the ethenyl bridge.

Without exception, saturation of the ethenyl bridge between the lactone and biphenyl moieties was detrimental (**2H**, **90H**, and **110H**), a result that is opposite to similar cases in the 6-benzyl ether series.[2]

The addition of a methyl group to the 4-position of **110** to give **6**, a compound that more closely resembles the HMG moiety of the substrate HMG-CoA, lowered potency 12-fold. An identical addition to **1** (a much less potent inhibitor) had little effect.[1] The contribution of the lactone

moiety stereochemistry to intrinsic inhibitory activity was shown earlier to be very important in that all of the activity resides in one of the enantiomers of the trans isomer.[1,2] This observation was extended and confirmed in this study by resolving lactones **100** and **110** to afford enantiomers **100(+)** and **110(+)**, each of which had about 2.8 times the intrinsic inhibitory potency of compactin.

Two independent chiral syntheses of **110(+)** have recently been published[4,13] and the in vivo activity will be described elsewhere.

Conclusion

Analysis of the intrinsic inhibitory potencies of the compounds evaluated in this study suggests that inhibitory binding to HMG-CoA reductase is augmented by (a) a 3- and 5-chloro or -methyl group on the central phenyl ring and (b) a 3′-methyl and 4′-halo group on the external phenyl ring, while binding is decreased by (c) increasing the distance between the two phenyl rings, (d) saturation of the ethenyl bridge between the biphenyl and lactone moieties, and (e) introduction of a methyl at the 4-position of the lactone ring. The absolute stereochemistry of the lactone ring must be the same as in compactin and mevinolin; in the present case, 4*R*,6*S*.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solutions were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (rotary evaporator). ^1H NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) 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 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 and used as received unless so indicated.

3-([1,1′-Biphenyl]-2-yl)-2-propenals (4). These compounds (**64–89**) were prepared by the general method described in ref 1; their physical properties are listed in Table II.

***trans*-6-[2-([1,1′-Biphenyl]-2-yl)ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-ones (5).** These compounds (**15, 23, 29, 90–115**) were elaborated from the corresponding propenals by the general method described in ref 1; their physical/biological properties are listed in Table III.

Hydrogenation of Lactones (5). Lactones **5** were hydrogenated over Rh/C in an analogous manner to the procedure described in ref 1; their physical/biological properties are listed in Table III (**2H, 90H,** and **110H**).

(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)-ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-4-methyl-2*H*-pyran-2-one (6). (a) 6-(3,3′,5-Trimethyl-4′-fluoro[1,1′-biphenyl]-2-yl)-4-hydroxy-5-hexen-2-one (6a). 2-Acetoxypropene (1.8 g, 18 mmol) and tributyltin methoxide (4.8 g, 15 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 **75** (3.2 g, 12 mmol) was added and the reaction mixture was stirred on a steam bath under N_2 for 4 h. The clear reaction mixture was then cooled, treated with malonic acid (600 mg, 5.8 mmol) in Et_2O (25 mL), and refluxed for 30 min. After cooling to −20 °C, the reaction mixture was filtered and the collected precipitate was washed with Et_2O (4 × 20 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) provided **6a** (3.9 g, 100%) as a thick yellow oil; NMR δ 2.06 (3 H, s), 2.3 (9 H, br s), 2.43 (2 H, d, J = 7 Hz), 4.4–4.65 (H, m), 5.36 (H, dd, J = 16.5 and 6 Hz), 6.46 (H, d, J = 16.5 Hz), 6.85–7.2 (5 H, m). Anal. ($C_{21}H_{23}FO_2$) C; H: calcd, 7.10; found, 7.54.

6-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)-2-oxo-5-hexen-4-yl 2-Bromoacetate (6b). 2-Bromoacetyl bromide (83 μL, 1.0 mmol) was added to a stirred solution of **6a** (300 mg, 0.92 mmol) and pyridine (81 μL, 1.0 mmol) in Et_2O (20 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) and additional Et_2O (100 mL). The organic layer was separated and washed with 1 N HCl (50 mL), H_2O (2 × 100 mL), and saturated brine, dried, filtered, and evaporated. The residual oil was chromatographed on silica gel. Elution with CH_2Cl_2–acetone (99:1, v/v) provided **6b** (270 mg, 66%) as a viscous, pale yellow oil; NMR δ 2.1 (3 H, s), 2.3 (9 H, br s), 2.35–2.75 (2 H, m), 3.7 (2 H, s), 5.36 (H, dd, J = 16.5 and 6 Hz), 5.55–5.8 (H, m), 6.6 (H, d, J = 16.5 Hz), 6.9–7.2 (5 H, m).

Compound 6. A solution of **6b** (250 mg, 0.56 mmol) in dry THF (10 mL) was added dropwise to a vigorously stirred slurry of activated Zn dust (60 mg, 0.85 mmol), CuBr (10 mg, 0.07 mmol), Et_2AlCl (25% solution in hexane; 0.34 mL, 0.6 mmol), and dry THF (5 mL) under N_2 at 20 °C. Stirring was continued for 5 h before quenching with pyridine (1 mL) followed by addition of H_2O (100 mL) and Et_2O extraction (3 × 50 mL). The combined Et_2O extracts were washed with 1 N HCl (3 × 50 mL), H_2O (2 × 100 mL) and saturated brine, then dried, filtered, and evaporated, leaving a golden glass (200 mg) which was a mixture of the cis and trans isomers of **6**. The isolation of the pure trans isomer was accomplished by HPLC on a Whatman M9/50 Partisil PAC column (10 × 20 mg injections). Elution with *i*-PrOH–hexane (1:20, v/v) at 8 mL/min provided **6** (70 mg, 34%) as a clear colorless glass. Elution times on this column under these conditions were 20 min for the trans isomer and 26.4 min for the cis isomer; NMR δ 1.35 (3 H, s), 1.4–2.0 (2 H, m), 2.28 (3 H, s), 2.35 (6 H, s), 2.4–2.8 (2 H, m), 5.0–5.4 (H, m), 5.4 (H, dd, J = 16.5 and 6 Hz), 6.6 (H, d, J = 16.5 Hz), 6.9–7.2 (5 H, m).

4-Bromo-2-(bromomethyl)-1-fluorobenzene (8). To a refluxing solution of 5-bromo-2-fluorotoluene (3.8 g, 20 mmol) in CCl_4 (30 mL) illuminated with a 275-W UV-sunlamp, a solution of Br_2 (1.1 mL, 20 mmol) in CCl_4 (30 mL) was added dropwise. Refluxing and irradiation were continued for an additional 0.5 h, and then the clear pale amber solution was concentrated. Distillation of the residue provided **8** as a clear colorless oil (4.3 g, 80%); bp 126–136 °C (15 mm); NMR δ 4.38 (2 H, s), 6.6–7.7 (3 H, m).

2-(Acetoxymethyl)-4-bromo-1-fluorobenzene (9). Anhydrous sodium acetate (1.65 g, 20 mmol) was added to a solution of **8** (3.9 g, 14.6 mmol) in DMF (25 mL) and the reaction mixture was stirred under N_2 on a steam bath for 11 h. The reaction mixture was cooled and distributed between H_2O (200 mL) and Et_2O (100 mL). The organic layer was separated and washed with H_2O (3 × 100 mL), dried, filtered, and evaporated, leaving **9** as a nearly colorless oil (3.2 g, 100%); NMR δ 2.08 (3 H, s), 5.08 (2 H, s), 6.7–7.9 (3 H, m).

5-Bromo-2-fluorobenzyl Alcohol (10). A solution of **9** (3.2 g, 14.5 mmol), EtOH (20 mL), and 1 N NaOH (20 mL, 20 mmol) was stirred at reflux under N_2 for 1.5 h. The reaction mixture was cooled and distributed between H_2O (150 mL) and Et_2O (150 mL). The organic layer was separated and washed with H_2O (2 × 100 mL) and dried and the clear faint yellow solution was evaporated. Distillation of the residue provided **10** as a clear colorless oil (1.7 g, 57%); bp 82–87 °C (0.4 mm); NMR δ 3.3 (H, br s), 4.6 (2 H, s), 6.81 (H_3, t, J = 9 Hz), 7.15–7.37 (H_4, m), 7.44 (H_6, dd, J = 3 and 6 Hz).

4-Bromo-1-fluoro-2-[[[(1,1-dimethylethyl)dimethylsilyl]-oxy]methyl]benzene (11). A mixture of **10** (1.7 g, 8.3 mmol), *tert*-butyldimethylsilyl chloride (1.8 g, 12 mmol) and imidazole (1.6 g, 24 mmol) in dry DMF (15 mL) was stirred under N_2 at 22 °C for 20 h. The mixture was poured into H_2O (200 mL) and extracted with Et_2O (2 × 75 mL). The organic extracts were combined and washed with 1 N HCl (100 mL), H_2O (2 × 100 mL), and saturated $NaHCO_3$ (100 mL), dried, filtered, and evaporated. The residual oil was chromatographed on silica gel (hexane) to yield **11** (2.03 g, 77%); NMR δ 0.1 (6 H, s), 0.93 (9 H, s), 4.73 (2 H, s), 6.82 (H_3, t, J = 9 Hz), 7.15–7.37 (H_4, m), 7.55 (H_6, dd, J = 3 and 6 Hz). Anal. ($C_{13}H_{20}BrFOSi$) H; C: calcd, 48.90; found, 47.84.

(*E*)-3-[4′-Fluoro-3,5-dimethyl-3′-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl][1,1′-biphenyl]-2-yl]-2-propenenitrile

(13) Prugh, J. D.; Rooney, C. S.; Deana, A. A.; Ramjit, H. G. *Tetrahedron Lett.* **1985**, 2947.

(13). A Grignard reagent, freshly prepared from 11 (2.0 g, 6.4 mmol) and magnesium turnings (185 mg, 7.5 mmol) in dry THF (6 mL), was filtered into a dry, N_2-purged flask. A 1.33 M solution of $ZnBr_2$ in THF (3 Å sieve dried, 2.52 mL, 3.36 mmol) was added over a 2-min period with vigorous stirring. After ca. 5 min a mixture of 12[4] (1.26 g, 5.4 mmol) and bis(triphenylphosphine)-nickel dichloride (100 mg, 0.16 mmol) was added to the gray slurry and the resultant red-brown mixture was stirred at 35 °C under N_2 for 4.5 h. The reaction mixture was quenched with 1 N HCl (100 mL) and extracted into EtOAc (125 mL). The organic phase was washed with H_2O (2 × 100 mL), dried, filtered, and evaporated, leaving 13 as a brown oil [R_f of 13 0.42 vs. 0.35 for 12 on TLC (silica, EtOAc–hexane (1:10))]. The residual oil was chromatographed on silica gel (EtOAc–hexane (1:10)) to yield 13 (1.4 g, 68%); NMR δ 0.13 (6 H, s), 0.94 (9 H, s), 2.35 (3 H, s), 2.42 (3 H, s), 4.84 (2 H, s), 5.22 (H, d, J = 17 Hz), 6.98–7.39 (6 H, m).

(*E*)-3-[4′-Fluoro-3,5-dimethyl-3′-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl][1,1′-biphenyl]-2-yl]-2-propenal (14). This compound was prepared by Dibal reduction of 13 by using the procedure described in ref 1 and obtained in 72% yield after chromatography on silica gel (CH_2Cl_2) as a pale yellow viscous oil; NMR δ 0.09 (6 H, s), 0.91 (9 H, s), 2.36 (3 H, s), 2.46 (3 H, s), 4.81 (2 H, s), 6.19 (H, dd, J = 7 and 15 Hz), 6.98–7.46 (6 H, m), 9.45 (H, d, J = 7 Hz).

Methyl (*E*)-7-[4′-Fluoro-3,5-dimethyl-3′-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl][1,1′-biphenyl]-2-yl]-3,5-dihydroxy-6-heptenoate (15a). The 5-hydroxy-3-keto ester (prepared by condensation of aldehyde 14 with the dianion of methyl acetoacetate as described in ref 1; 1.0 g, 1.96 mmol) was dissolved in dry THF (5 mL) under N_2 and then treated with triethylborane (1 M in THF, 2.9 mL, 2.9 mmol). After aging for 5 min, the reaction mixture was cooled to −98 °C (MeOH–liquid N_2 bath). Sodium borohydride (85 mg, 2.25 mmol) was added followed by MeOH (2 mL) over 5 min. After stirring for an additional 0.5 h, the reaction mixture was allowed to warm to −60 °C and then was quenched by the careful addition of 30% H_2O_2 (4 mL) in H_2O (10 mL). The mixture was stirred vigorously at ambient temperature for 0.5 h and then distributed between 1 N HCl (50 mL) and EtOAc (100 mL). The organic layer was washed with H_2O (2 × 50 mL), dried, filtered, and evaporated to provide **15a** (900 mg, 89%) as a pale yellow gum [R_f of **15a** 0.15 vs. 0.30 for precursor keto compound on TLC (silica, $CHCl_3$–MeOH (99:1))]; ^1H NMR shows an 11:1 ratio of erythro vs. threo; NMR δ 0.12 (6 H, s), 0.93 (9 H, s), 1.42–1.61 (2 H, m), 2.32 (6 H, s), 2.34–2.46 (2 H, m), 3.70 (3 H, s), 4.05–4.15 (H, m), 4.3–4.4 (H, m), 4.7–4.85 (2 H, m), 5.29 (H, dd, J = 7 and 16 Hz), 6.43 (H, d, J = 16 Hz), 6.95–7.40 (6 H, m). The threo isomer can be detected by examination of the vinyl protons in the NMR; δ 5.36 (H, dd, J = 7 and 16 Hz) and 6.50 (H, d, J = 16 Hz).

***trans*-(*E*)-6-[2-[4′-Fluoro-3′-(hydroxymethyl)-3,5-dimethyl[1,1′-biphenyl]-2-yl]ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2*H*-pyran-2-one (15).** A solution of the *tert*-butyldimethylsilyl ether (prepared from **15a** by ester hydrolysis and subsequent lactonization as described in ref 1; 420 mg, 0.087 mmol) in THF (5 mL) was treated with tetrabutylammonium fluoride (1 M in THF, 2.5 mL, 2.5 mmol). After the mixture was stirred at 20 °C for 5 min, 1 N HCl (100 mL) was added and the product was extracted into Et_2O (125 mL). The organic layer was washed with H_2O (2 × 100 mL), dried, filtered, and evaporated to provide **15** as a faint yellow gum (300 mg, 90%); homogenous on TLC [R_f 0.20 vs. 0.42 for the silyl ether (silica, $CHCl_3$–MeOH (19:1))] and HPLC [time of elution was 5.36 min with a flow rate of 4 mL/min using 20% 2-propanol/hexane on a Whatman Partisil PXS 10/25 PAC column]. An analytical sample was crystallized from *n*-BuCl: mp 137–138 °C; NMR δ 1.7–1.95 (2 H, m), 2.33 (6 H, s), 2.45–2.75 (2 H, m), 4.05–4.1 (H, m), 4.7–4.85 (2 H, m), 5.12–5.18 (H, m), 5.4 (H, dd, J = 7 and 15 Hz), 6.53 (H, d, J = 15 Hz), 6.95–7.35 (6 H, m).

Methyl 3-[2,4-Dichloro-6-(dimethoxymethyl)phenyl]-propionate (17). Ozone was bubbled into a stirred solution of 16[2] (4.15 g, 12.6 mmol) in CH_3OH (40 mL) and CH_2Cl_2 (40 mL) at −78 °C until the color of the solution turned green. After the excess ozone was expelled with a stream of nitrogen gas, dimethyl sulfide (1.20 g, 18.9 mmol) was added and the resulting mixture was warmed to 20 °C and stirred for 16 h. The reaction mixture was poured into cold H_2O and extracted with Et_2O. The ethereal extract was dried, filtered, and concentrated to leave a residual oil which was dissolved in CH_3OH (25 mL). Concentrated H_2SO_4 (0.2 mL) was added to this solution and the resulting mixture was heated at reflux for 7 h. It was cooled to 20 °C, poured into cold H_2O, and extracted with Et_2O. The ethereal extract was dried, filtered, and evaporated to yield 17 (2.80 g, 72%) as an oil: NMR δ 2.3–2.7 (2 H, m), 2.9–3.3 (2 H, m), 3.32 (6 H, s), 3.70 (3 H, s), 5.44 (H, s), 7.30 (H, d, J = 2 Hz), 7.44 (H, d, J = 2 Hz).

3-[2,4-Dichloro-6-(dimethoxymethyl)phenyl]propanol (18). A solution of 17 (2.80 g, 9.11 mmol) in Et_2O (10 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (0.50 g, 13.2 mmol) in Et_2O (50 mL) at 0 °C. After the addition was complete, the resulting mixture was stirred at 20 °C for 0.5 h and then heated at reflux for 1 h. The reaction flask was chilled in an ice bath and treated successively with H_2O (0.5 mL), 20% NaOH (0.5 mL), and H_2O (1.5 mL). The resulting mixture was stirred at 20 °C for 1 h. The solid precipitates were removed by filtration. Evaporation of the filtrate gave 18 (2.25 g, 88%) as an oil: NMR δ 1.6–2.0 (2 H, m), 2.6–3.0 (2 H, m), 3.30 (6 H, s), 3.62 (2 H, t, J = 6 Hz), 5.42 (H, s), 7.30 (H, d, J = 2 Hz), 7.41 (H, d, J = 2 Hz).

3,5-Dichloro-2-[3-(phenylthio)propyl]benzaldehyde (19). To a stirred solution of tosyl chloride (2.28 g, 12 mmol) in pyridine (6 mL) was added a solution of 18 (2.25 g, 8.06 mmol) in pyridine (4 mL) with cooling in an ice bath. After completion of the addition, the resulting mixture was stirred at 0 °C for 0.5 h and then stored in a freezer for 15 h. It was poured into cold H_2O and extracted with Et_2O. The ethereal extract was washed with aqueous cupric sulfate solution, dried, filtered, and evaporated to give the tosylate of 18 as a brownish oil: NMR δ 1.7–2.1 (2 H, m), 2.42 (3 H, s), 2.7–3.0 (2 H, m), 3.30 (6 H, s), 4.12 (2 H, t, J = 6 Hz), 5.38 (H, s), 7.25 (H, d, J = 2 Hz), 7.28 (2 H, d, J = 8 Hz), 7.40 (H, d, J = 2 Hz), 7.74 (2 H, d, J = 8 Hz).

The above tosylate was dissolved in CH_3OH (5 mL) and added to a stirred solution of sodium thiophenoxide prepared by mixing sodium methoxide (0.54 g, 10 mmol) and thiophenol (1.10 g, 10 mmol) in CH_3OH (15 mL). The resulting mixture was stirred at 20 °C under a N_2 atmosphere for 0.5 h and then heated at reflux for 1 h. After cooling, it was poured into cold H_2O and extracted twice with Et_2O. The combined extracts were dried, filtered, and concentrated to afford a brownish oil which was dissolved in acetone (25 mL) and H_2O (15 mL). After the addition of concentrated H_2SO_4 (0.5 mL), the resulting mixture was heated at reflux for 16 h. After cooling, it was poured into cold H_2O and extracted twice with Et_2O. The combined extracts were washed with H_2O, dried, filtered, and evaporated to leave an oily residue which was purified by column chromatography (silica gel). Elution of the column with CH_2Cl_2–hexane (1:1, v/v) gave 19 (1.65 g, 40% overall from 16) as an oil: IR (neat) 1690 cm^{-1}; NMR δ 1.7–2.1 (2 H, m), 3.02 (2 H, t, J = 7 Hz), 3.2–3.4 (2 H, m), 7.2–7.5 (5 H, m), 7.58 (H, d, J = 2 Hz), 7.68 (H, d, J = 2 Hz), 10.20 (H, s).

3,5-Dichloro-2-[3-(phenylthio)propyl]benzophenone (20). A solution of 19 (1.65 g, 5.1 mmol) in Et_2O (5 mL) was added to a Grignard reagent, freshly prepared from phenyl bromide (1.48 g, 9.42 mmol) and magnesium turnings (0.194 g, 8 mmol) in Et_2O (15 mL), at 0 °C under an N_2 atmosphere. The resulting mixture was stirred at 0 °C for 0.5 h, then warmed at 20 °C, and stirred for 1 h. The reaction mixture was recooled to 0 °C and treated with HCl (2 N, 10 mL) added dropwise. After stirring for 0.5 h, the reaction mixture was diluted with H_2O and extracted with Et_2O. The ethereal extract was washed with H_2O, dried, filtered, and evaporated to provide 3,5-dichloro-2-[3-(phenylthio)-propyl]benzhydrol as a yellow oil: NMR δ 1.4–2.0 (2 H, m), 2.40 (H, br s), 2.6–3.0 (4 H, m), 5.88 (H, s), 7.1–7.4 (11 H, m), 7.40 (H, d, J = 2 Hz).

Trifluoroacetic anhydride (1.2 mL, 8.5 mmol) was added to a stirred solution of Me_2SO (0.81 mL, 11.4 mmol) in CH_2Cl_2 (8 mL) at −78 °C under N_2 atmosphere. The resulting mixture was stirred at −78 °C for 15 min and treated with a solution of the above benzhydrol in CH_2Cl_2 (3 mL) added dropwise. The resulting mixture was stirred at −78 °C for 0.5 h, treated with triethylamine (2.2 mL), stirred at −78 °C for 0.5 h, and then warmed to 20 °C. The reaction mixture was poured into cold H_2O and extracted with Et_2O. The ethereal extract was washed with 5% $NaHCO_3$, dried, filtered, and concentrated to yield an oily residue which was purified by column chromatography (silica gel). Elution of

the column with petroleum ether–CH_2Cl_2 (2:1, v/v) provided **20** (1.80 g, 84% overall) as a yellow oil: IR (neat) 1662 cm^{-1}; NMR δ 1.6–2.2 (2 H, m), 2.6–3.0 (4 H, m), 7.0–7.8 (12 H, m).

1-Benzyl-3,5-dichloro-2-[3-(phenylthio)propyl]benzene (21). A mixture of **20** (1.65 g, 4.11 mmol), hydrazine (97%, 0.45 g, 14 mmol), and KOH (0.79 g, 14 mmol) in diethylene glycol (6 mL) was heated at 110 °C for 1 h to distill off the H_2O. The mixture was then heated at 200–205 °C for 15 h. After cooling, the reaction mixture was poured into cold H_2O, acidified with 2 N HCl, and extracted twice with Et_2O. The combined extracts were washed with H_2O, dried, filtered, and evaporated to leave an oily residue which was purified by column chromatography (silica gel). Elution of the column with hexane–CH_2Cl_2 (2:1, v/v) gave **21** (0.88 g, 55%) as an oil: NMR δ 1.6–2.0 (2 H, m), 2.7–3.1 (4 H, m), 3.93 (2 H, s), 6.9–7.4 (12 H, m).

3-(6-Benzyl-2,4-dichlorophenyl)propanal (22). Powdered *N*-chlorosuccinimide (1.27 g, 7.95 mmol) was added in one portion to a stirred solution of **21** (3.0 g, 7.74 mmol) in CCl_4 (50 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 4 h. The solid precipitates were filtered off, and the filtrate was concentrated to leave an oily residue. This residue was dissolved in THF (50 mL) and H_2O (1.5 mL) followed by the addition of $CuBr_2$ (1.78 g, 8 mmol) and CuO (0.64 g, 8 mmol) and heated at reflux for 10 min. After cooling, the solid precipitates were collected by filtration, and the filtrate was distributed between Et_2O and H_2O. The organic phase was separated, dried, filtered, and evaporated to yield a residue which was purified by column chromatography (silica gel). Elution of the column with hexane–CH_2Cl_2 (2:1 v/v) produced **22** (1.80 g, 74%) as a pale yellow oil: NMR δ 2.2–2.4 (2 H, m), 2.7–3.0 (2 H, m), 3.97 (2 H, s), 7.0–7.6 (7 H, m), 9.65 (H, s).

3-[2-[2-(4-Chlorophenyl)ethenyl]-4,6-dimethylphenyl]-2-propenal (28). (a) 3-(2-Bromo-4,6-dimethylphenyl)-2-propenoic Acid (26). A solution of $NaNO_2$ (14 g) in H_2O (60 mL) was added dropwise to a suspension of **25**[14] (40 g, 200 mmol) in H_2O (120 mL) and HCl (12 N, 160 mL) with vigorous stirring at 0 °C. The clear, pale yellow solution was added dropwise with vigorous stirring to a mixture of ethyl acrylate (24 mL, 240 mmol), H_2O (100 mL), acetone (200 mL), $CuCl_2$ (6 g), and NaOAc·$3H_2O$ (120 g) at 0 °C. The resulting clear, pale green reaction mixture was then stirred at 40–50 °C for 8 h during which time N_2 evolution took place and a two-phase mixture formed. After dilution with H_2O (200 mL), the resulting heavy amber oil was extracted with Et_2O (150 mL). The extract was washed with H_2O (3 × 100 mL) and saturated brine (200 mL), dried ($MgSO_4$), filtered, and evaporated.

The crude ethyl α-chloropropionate was treated with EtOH (500 mL) and KOH (68 g, 1.2 mol) heated at reflux for 16 h. The mixture was cooled, diluted with H_2O (2 L), and extracted with Et_2O (3 × 200 mL). The clear pale amber aqueous layer was separated and acidified. The moist solid was crystallized from HOAc–H_2O (2:1, v/v, 300 mL) to provide **26** (21 g, 41%): mp 186–188 °C; NMR (Me_2SO-d_6) δ 2.26 (3 H, s), 2.32 (3 H, s), 6.15 (H, d, J = 16.5 Hz), 7.13 (H, s), 7.36 (H, s), 7.6 (H, d, J = 16.5 Hz). Anal. ($C_{11}H_{11}BrO_2$) C, H.

If the hydrolysis was run at 20 °C, the α-chloropropionic acid was obtained (84%), mp 127–128.5 °C. An analytical sample was crystallized from *n*-BuCl: mp 129–130.5 °C; NMR δ 2.25 (3 H, s), 2.4 (3 H, s), 3.35 (H, dd, J = 13.5 and 6 Hz), 3.55 (H, dd, J = 13.5 and 6 Hz), 4.8 (H, dd, J = 7.5 and 4 Hz), 6.95 (H, br s), 7.25 (H, br s). Anal. ($C_{11}H_{12}BrClO_2$) C, H.

(b) 3-[2-[2-(4-Chlorophenyl)ethenyl]-4,6-dimethyl]-2-propenoic Acid (27). A mixture of **26** (765 mg, 3 mmol), 4-chlorostyrene (360 μL, 3 mmol), TEA (900 μL, 6.5 mmol), $Pd(OAc)_2$ (10 mg), and triphenylphosphine (25 mg) was stirred under N_2 at 95–100 °C for 48 h. The dark glassy mixture was dissolved in DMF (50 mL) and then distributed between Et_2O (200 mL) and 6 N HCl (100 mL). The organic layer was separated and washed with H_2O (3 × 100 mL) and saturated brine (100 mL), dried, filtered, and evaporated. The residue was chromatographed on silica gel. Elution with CH_2Cl_2–MeOH (40:1 v/v, 1.2 L) provided crude product which was crystallized from HOAc–H_2O (5:1, v/v, 12 mL) to yield **27** (450 mg, 48%): mp 167–169 °C; NMR (Me_2SO-d_6) δ 2.27 (3 H, s), 2.3 (3 H, s), 5.9 (H, d, J = 16.5 Hz), 6.95–7.65 (8 H, m), 7.8 (H, d, J = 16.5 Hz). Anal. ($C_{19}H_{17}ClO_2$) C, H.

(c) Compound 28. A solution of the acid chloride of **27** (prepared from 625 mg of **27** and $SOCl_2$) in acetone (35 mL) was treated with triphenylphosphine (1.1 g, 4.2 mmol) followed by bis(triphenylphosphine)copper(I) tetrahydroborate (1.3 g, 2.2 mmol). After 1 h the white tris(triphenylphosphine)copper(I) chloride was filtered off and the acetone was evaporated. The residue was extracted with Et_2O (2 × 30 mL). Evaporation of the Et_2O left a residue which was chromatographed on silica gel. Elution with CH_2Cl_2 provided **28** (500 mg, 84%). Crystallization from cyclohexane provided an analytical sample: mp 91–92 °C; NMR δ 2.3 (6 H, s), 6.3 (H, dd, J = 16.5 and 7.5 Hz), 6.7–7.4 (8 H, m), 7.66 (H, d, J = 16.5 Hz), 9.75 (H, d, J = 7.5 Hz). Anal. ($C_{19}H_{17}ClO$) C, H.

[1,1′-Biphenyl]-2-carboxaldehydes (3). Method 1. 2,4-Dichloro-6-methoxybenzaldehyde (33). Potassium carbonate (3.8 g, 28 mmol) was added to a solution of **30** (4.75 g, 25 mmol) in DMF (50 mL) at 50 °C followed 0.5 h later by an excess of methyl iodide (6 mL, 50 mmol). The mixture was stirred at 50 °C for 1 h, cooled, and poured into H_2O (400 mL). The crude ether separated as a white powder, which was collected, washed well with H_2O, and air-dried to yield **33** (5.2 g, 100%): mp 110–111 °C; NMR δ 3.91 (3 H, s), 6.90 (H, d, J = 1.5 Hz), 7.06 (H, d, J = 1.5 Hz), 10.41 (H, s).

***N*-(2-Hydroxy-1,1-dimethylethyl)-2,4-dichloro-6-methoxybenzamide (35).** A suspension of **33** (3 g, 15 mmol) and *N*-bromosuccinimide (3.6 g, 20 mmol) in CCl_4 (30 mL) was illuminated with a 150-W flood lamp under N_2 with vigorous stirring on a steam bath for 7 min. The cloudy mixture was cooled to 0 °C, diluted with CH_2Cl_2 (30 mL), and treated dropwise with a solution of 2-amino-2-methylpropanol (3 mL, 30 mmol) in CH_2Cl_2 (30 mL). The ice bath was removed and the mixture was stirred at 20 °C for 20 h. The reaction mixture was filtered, and the collected solids were washed with additional CH_2Cl_2 (50 mL). The clear filtrates were combined and washed with H_2O (100 mL), 5% HCl (100 mL), 5% NaOH (100 mL), H_2O (100 mL), and brine, dried, filtered, and evaporated in vacuo to provide **35** as a white powder (3.6 g, 82%), mp 130–132 °C. Crystallization from hexane–toluene (10:8, v/v) provided an analytical sample: mp 131–132 °C; NMR δ 1.36 (6 H, s), 3.75 (2 H, s), 3.83 (3 H, s), 6.81 (H, d, J = 1.5 Hz), 7.20 (H, d, J = 1.5 Hz). Anal. ($C_{12}H_{15}Cl_2NO_3$) C, H, N.

2-(2,4-Dichloro-6-methoxyphenyl)-4,5-dihydro-4,4-dimethyloxazole (36). Benzamide **35** (5.5 g, 18.8 mmol) was treated dropwise with $SOCl_2$ (5.5 mL) and stirred at 20 °C for 30 min. Dry Et_2O (100 mL) was added, the mixture was stirred for an additional 1 h, and the oxazoline hydrochloride precipitate was collected by filtration. The salt was neutralized with 20% NaOH to afford an alkaline mixture which was extracted with Et_2O. The ethereal extract was dried and concentrated to give oily **36** (3.6 g, 70%), which crystallized on standing: mp 47–50 °C; NMR δ 1.4 (6 H, s), 3.83 (3 H, s), 4.1 (2 H, s), 6.82 (H, d, J = 1.5 Hz), 7.06 (H, d, J = 1.5 Hz). Anal. ($C_{12}H_{13}Cl_2NO_2$) C, H, N.

Alternate Preparation of 35 from 30. 4,6-Dichlorosalicylic Acid (31). This acid was prepared by the general method of Campaigne and LeSuer[15] for oxidation of the corresponding aldehydes via Ag_2O (93%), mp 195–196 °C (lit.[16] mp 200 °C).

Methyl 2,4-Dichloro-6-methoxybenzoate (32). This compound was prepared analogously to **33**, with **31** (9.9 g, 47.8 mmol) and 2 equiv of K_2CO_3 as the starting material, yield (11.1 g, 99%), mp 52–54 °C. Crystallization from petroleum ether provided an analytical sample: mp 58–59 °C; NMR δ 3.82 (3 H, s), 3.91 (3 H, s), 6.83 (H, d, J = 1.5 Hz), 7.02 (H, d, J = 1.5 Hz). Anal. ($C_9H_8Cl_2O_3$) C, H.

2,4-Dichloro-6-methoxybenzoic Acid (34). Methyl ester **32** (1 g, 4 mmol) was stirred at 100 °C with 4-(aminomethyl)piperidine (2 mL) for 1.5 h (the demethylation requires about 6.5–7 h at 80

(14) Wheeler, A. S.; Thomas, R. E. *J. Am. Chem. Soc.* **1928**, *50*, 2286.

(15) Campaigne, E.; LeSuer, W. M. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 919.

(16) Baine, O.; Adamson, G. F.; Barton, J. W.; Fitch, J. L.; Swayampati, D. R.; Jeskey, H. *J. Org. Chem.* **1954**, *19*, 510.

°C). After the mixture cooled to ambient temperature, 2 N HCl (50 mL) was added and the mixture was cooled to 0 °C with stirring. The acid was collected as a white powder, washed with H_2O, and air-dried to yield **34** (800 mg, 90%): mp 163–165 °C; NMR δ 3.87 (3 H, s), 6.96 (H, d, J = 1.5 Hz), 7.04 (H, d, J = 1.5 Hz).

Alternate Preparation of 34 from 33. This acid was prepared by a slight modification of the general method of Herriott and Picker[17] for oxidation with "purple benzene". Potassium permanganate (8.7 g, 55 mmol) was added in three portions at 3 h intervals to a vigorously stirred mixture of **33** (3.4 g, 16.3 mmol), H_2O (50 mL), toluene (100 mL), and n-$Bu_4N^+I^-$ (500 mg) at 20 °C. After the purple mixture was stirred for a total of 8 h, $NaHSO_3$ was added, followed by acidification with HCl. The light yellow organic layer was separated, washed with saturated brine, and dried. Evaporation of the solvent provided **34** (2.4 g, 67%), mp 162–164 °C.

Alternate Preparation of 35 from 34. The acid chloride of **34** (prepared from **34**; 2.4 g, 10.8 mmol and $SOCl_2$) was dissolved in CH_2Cl_2 (10 mL) and added dropwise to a solution of 2-amino-2-methylpropanol (2.1 mL, 22 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The ice bath was removed and the mixture was stirred at 20 °C for 20 h. The reaction mixture was worked up as in **35** vida supra to give **35** (1.9 g, 60%), mp 132–133 °C.

2-(3,5-Dichloro-4′-fluoro[1,1′-biphenyl]-2-yl)-4,5-dihydro-4,4-dimethyloxazole (37c). A solution of (4-fluorophenyl)-magnesium bromide, prepared from 4-bromofluorobenzene (4.4 g, 25 mmol) and magnesium (0.6 g, 25 mmol), in dry Et_2O (40 mL) was added dropwise to a stirred solution of **36** (4.4 g, 16 mmol) in dry THF (150 mL) under N_2 at 20 °C. Stirring of the solution was continued for 20 h at reflux, the solution was cooled, and then the reaction mixture was quenched by the addition of saturated ammonium chloride solution. The resulting mixture was extracted with Et_2O (2 × 50 mL), dried, filtered, and evaporated. The residue was chromatographed on silica gel ($CHCl_3$) to provide **37c** (4.6 g, 85%), homogenous by HPLC. An analytical sample was crystallized from petroleum ether: mp 93–95 °C; NMR δ 1.16 (6 H, s), 3.83 (2 H, s), 6.9–7.5 (6 H, m). Anal. ($C_{17}H_{14}Cl_2FNO$) C, H, N.

2-(3,5-Dichloro[1,1′-biphenyl]-2-yl)-4,5-dihydro-4,4-dimethyloxazole (37a): yield (95%). An analytical sample was crystallized from petroleum ether: mp 92–94.5 °C; NMR δ 1.17 (6 H, s), 3.85 (2 H, s), 7.13–7.33 (7 H, m). Anal. ($C_{17}H_{15}Cl_2NO$) C, H, N.

2-(3,4′,5-Trichloro[1,1′-biphenyl]-2-yl)-4,5-dihydro-4,4-dimethyloxazole (37b): yield (34%); NMR δ 1.2 (6 H, s), 3.9 (2 H, s), 7.2–7.5 (6 H, m).

2-[2,4-Dichloro-6-(2-phenylethyl)phenyl]-4,5-dihydro-4,4-dimethyloxazole (37d): yield (57%); NMR δ 1.4 (6 H, s), 2.9 (4 H, s), 4.1 (2 H, s), 7.0–7.3 (7 H, m).

2-(3,5-Dichloro-4′-fluoro[1,1′-biphenyl]-2-yl)-4,5-dihydro-3,4,4-trimethyloxazolium Iodide (38c). A solution of **37c** (4.6 g, 13.6 mmol) and methyl iodide (7 mL) in nitromethane (30 mL) was stirred on a steam bath for 16 h. The cooled reaction mixture was diluted with Et_2O (200 mL), and after cooling in an ice bath, the crystalline product was collected to give 6 g (92%) of **38c**, mp 214–216 °C dec. Crystallization from CH_3CN–Et_2O (1:3, v/v) provided an analytical sample: mp 218–219.5 °C dec; NMR δ 1.5 (3 H, s), 1.76 (3 H, s), 3.2 (3 H, s), 5.1 (2 H, s), 7.2–7.7 (6 H, m). Anal. ($C_{18}H_{17}Cl_2FINO$) C, H, N.

2-(3,5-Dichloro[1,1′-biphenyl]-2-yl)-4,5-dihydro-3,4,4-trimethyloxazolium iodide (38a): yield (100%). An analytical sample was crystallized from CH_3CN–Et_2O: mp 207–207.5 °C dec; NMR (Me_2SO-d_6) δ 1.2 (3 H, s), 1.53 (3 H, s), 3.3 (3 H, s), 4.8 (H, d, J = 11 Hz), 5.1 (H, d, J = 11 Hz), 7.35–7.7 (5 H, m), 7.36 (H, d, J = 1.5 Hz), 8.16 (H, d, J = 1.5 Hz); NMR ($CDCl_3$) δ 1.43 (3 H, s), 1.8 (3 H, s), 3.13 (3 H, s), 4.95 (H, d, J = 11 Hz), 5.15 (H, d, J = 11 Hz), 7.3–7.7 (7 H, m). Anal. ($C_{18}H_{18}Cl_2INO$ (C, H, N).

2-(3,4′,5-Trichloro[1,1′-biphenyl]-2-yl)-4,5-dihydro-3,4,4-timethyloxazolium iodide (38b): yield (79%). An analytical sample was crystallized from CH_3CN–Et_2O: mp 229–230 °C dec; NMR δ 1.5 (3 H, s), 1.8 (3 H, s), 3.26 (3 H, s), 5.5 (H, d, J = 11 Hz), 5.23 (H, d, J = 11 Hz), 7.3–7.7 (6 H, m). Anal. ($C_{18}H_{17}Cl_3INO$) C, H, N.

2-[2,4-Dichloro-6-(2-phenylethyl)phenyl]-4,5-dihydro-3,4,4-trimethyloxazolium iodide (38d): yield (88%). An analytical sample was crystallized from CH_3CN–Et_2O: mp 186–187 °C dec; NMR δ 1.8 (3 H, s), 1.93 (3 H, s), 3.0 (3 H, s), 3.0–3.15 (4 H, m), 5.16 (H, d, J = 9 Hz), 5.46 (H, d, J = 9 Hz), 7.1–7.5 (7 H, m). Anal. ($C_{20}H_{22}Cl_2INO$) C, H, N.

3,5-Dichloro-4′-fluoro[1,1′-biphenyl]-2-carboxaldehyde (3c). A vigorously stirred suspension of **29c** (5.9 g, 12.3 mmol) in EtOH (50 mL) was treated portionwise with $NaBH_4$ (550 mg, 18 mmol). After stirring for 2 h at ambient temperature, the clear solution was diluted with 3 N HCl (100 mL) and stirred on a steam bath for 2 h. The reaction mixture was then cooled, diluted with H_2O (200 mL), and extracted with Et_2O (300 mL). The Et_2O extract was washed with H_2O (2 × 200 mL) and brine, then dried, filtered, and evaporated in vacuo to provide 2.72 g (82%) of **3c**, mp 66–68 °C. Crystallization provided an analytical sample: NMR δ 7.0–7.5 (6 H, m), 10.1 (H, s).

Method 2. *N*-[(2,4-Dichlorophenyl)methylene]-benzenamine (40c). A mixture of **39c** (150 g, 0.86 mol), freshly distilled aniline (75 mL, 0.86 mol) and toluene (300 mL) was refluxed under a Dean–Stark trap for 2 h. The light tan solution was then cooled and evaporated under reduced pressure. After the residue was dried in vacuo at 50 °C for 16 h, the yield was 213 g (99%), mp 87–89 °C (lit.[18] mp 89.5 °C).

***N*-[(2-Chlorophenyl)methylene]benzenamine (40a):** yield (90%) as a viscous oil; NMR δ 7.2–7.6 (8 H, m), 8.25–8.4 (H, m), 9.0 (H, s). Anal. ($C_{13}H_{10}CN$) C, H, N.

***N*-[(2,4-Difluorophenyl)methylene]benzenamine (40b):** yield (97%) as a tan liquid; NMR δ 6.5–7.4 (7 H, m), 8.0 (H, q, J = 8 and 2 Hz), 8.5 (H, s).

***N*-[(2-Chloro-4-methylphenyl)methylene]benzenamine (40d):** yield (100%) as a brown oil; NMR δ 2.34 (3 H, s), 7.1–7.6 (7 H, m), 8.14 (H, d, J = 7.5 Hz), 8.90 (H, s). Anal. ($C_{14}H_{12}CIN$) C, H, N.

***N*-[(4-Chloro-2-methylphenyl)methylene]benzenamine (40e):** yield (77%) after distillation via a Kugelrohr apparatus (oven temperature 160 °C, 0.5 mm) as a viscous oil; NMR δ 2.5 (3 H, s), 6.3–7.5 (7 H, m), 7.95 (H, d), 8.6 (H, s).

***N*-[(2,4-Dimethylphenyl)methylene]benzenamine (40f):** yield (100%) after vacuum distillation, bp 120–122 °C (0.2–0.25 mm) as a pale yellow oil; NMR δ 2.33 (3 H, s), 2.53 (3 H, s), 7.0–7.6 (7 H, m), 7.95 (H, d), 8.6 (H, s). Anal. ($C_{15}H_{15}N$) C, H, N.

***N*-[(2,5-Dimethylphenyl)methylene]benzenamine (40g):** yield (96%) after vacuum distillation, bp 155–157 °C (1.4 mm) as a pale yellow oil; NMR δ 2.33 (3 H, s), 2.47 (3 H, s), 7.1–7.5 (7 H, m), 8.0 (H, s), 8.78 (H, s). Anal. ($C_{15}H_{15}N$) C, H, N.

Bis(μ-acetato-*O*,*O*′)bis[3,5-dichloro-2-[(phenylimino)-methyl]phenyl-*C*,*N*]dipalladium (41c). A mixture of **40c** (58.2 g, 0.23 mol) and Pd(II) acetate (52.4 g, 0.23 mol) in HOAc (1 L) was stirred at reflux for 1 h. The turbid solution was cooled and poured into H_2O (4 L) to give **41c** as a red powder after drying in vacuo at 50 °C for 16 h (94.5 g, 98%). Crystallization from HOAc–H_2O (7:1, v/v) provided an analytical sample of **41c**: mp 203–205 °C; NMR δ 1.73 (3 H, s), 6.50 (H, d, J = 1.5 Hz), 6.97 (2 H, m), 7.12 (H, d, J = 1.5 Hz), 7.33 (3 H, m), 8.03 (H, s). Anal. ($C_{30}H_{22}Cl_4N_2O_4Pd_2$) C, H, N.

Bis(μ-acetato-*O*,*O*′)bis[3-chloro-2-[(phenylimino)-methyl]phenyl-*C*,*N*]dipalladium (41a): yield (92%), mp 102–110 °C. An analytical sample was prepared as in **41c**. Anal. ($C_{30}H_{22}Cl_2N_2O_4Pd_2$) C, H, N.

Bis(μ-acetato-*O*,*O*′)bis[3,5-difluoro-2-[(phenylimino)-methyl]phenyl-*C*,*N*]dipalladium (41b): yield (94%), mp 212–214 °C; NMR δ 1.8 (6 H, s), 6.0 (2 H, dd, J = 9 and 2 Hz), 6.5 (2 H, td, J = 9 and 2 Hz), 6.8–7.0 (4 H, m), 7.16–7.36 (6 H, m), 7.92 (2 H, s).

Bis(μ-acetato-*O*,*O*′)bis[3-chloro-5-methyl-2-[(phenylimino)methyl]phenyl-*C*,*N*]dipalladium (41d): yield (92%), mp 104–120 °C. An analytical sample was prepared as in **41c**. Anal. ($C_{32}H_{28}Cl_2N_2O_4Pd_2$) C, H, N.

Bis(μ-acetato-*O*,*O*′)bis[5-chloro-3-methyl-2-[(phenylimino)methyl]phenyl-*C*,*N*]dipalladium (41e): yield (75%)

(17) Herriott, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, 1511.

(18) Kadaba, P. K.; Fannin, N. F. *J. Heterocycl. Chem.* **1967**, *4*, 301.

as an orange powder; NMR δ 1.69 (3 H, s), 2.32 (3 H, s), 6.58 (H, d, J = 2 Hz), 6.9–7.1 (3 H, m), 7.3–7.5 (3 H, m), 7.80 (H, s).

Bis(μ-acetato-*O*,*O*')bis[3,5-dimethyl-2-[(phenylimino)methyl]phenyl-*C*,*N*]dipalladium (41f): yield (96%) as a yellow-orange powder; NMR δ 1.76 (3 H, s), 2.27 (3 H, s), 2.34 (3 H, s), 6.43 (H, s), 6.70 (H, s), 6.9–7.1 (2 H, m), 7.2–7.4 (3 H, m), 7.8 (H, s).

Bis(μ-acetato-*O*,*O*')bis[3,6-dimethyl-2-[(phenylimino)methyl]phenyl-*C*,*N*]dipalladium (41g): yield (75%) as a light yellow-orange powder.

Compound 3c. A solution of **41c** (8.29 g, 10 mmol) and triphenylphosphine (21.0 g, 80 mmol) in dry toluene (150 mL) was stirred for 30 min at ambient temperature under N_2. (4-Fluorophenyl)magnesium bromide, prepared from 4-bromofluorobenzene (15.4 g, 88 mmol) and magnesium (1.94 g, 80 mmol) in dry Et_2O (100 mL) under N_2 at ambient temperature, was added to the above solution in one portion and the resulting mixture was stirred for 1 h. After the addition of 6 N HCl (50 mL), the mixture was stirred for 1 h and then filtered. The filtrate was diluted with Et_2O (300 mL) and washed with saturated brine (3 × 200 mL), dried, filtered, and evaporated. The residue was chromatographed on a silica column (1 kg). Elution with Et_2O–hexane (1:39, v/v, 5.5 L) provided a forerun which was discarded. Continued elution with Et_2O–hexane (1:9, v/v, 5.7 L) gave **3c** (4.5 g, 84%), mp 73–74 °C.

Subsequent preparations of **3c** and all other 1,1'-biphenyl-2-carboxaldehydes (**3**) used various concentrations of CH_2Cl_2–hexane as eluant [R_f of **3c** 0.34 on TLC (silica, CH_2Cl_2–hexane (1:1))].

4-Fluoro-3,5-dimethylbromobenzene (59a). 4-Bromo-2,5-dimethylaniline (16.9 g, 0.085 mol) was added portionwise to a well-stirred solution of 40 mL of fluoroboric acid (48–50%) in H_2O (60 mL) and EtOH (50 mL). After cooling to ~5 °C, a solution of $NaNO_2$ (5.87 g, 0.085 mol) in H_2O (40 mL) was added dropwise. The thick mixture was stirred with cooling for 1 h and then filtered; the white solid was washed with 50 mL of cold EtOH followed by 50 mL of Et_2O and air-dried.

The dried solid was placed in a flask equipped with a distilling head and heated in an oil bath at 110–200 °C with stirring for 1 h and at 200 °C for 30 min. After cooling, the mixture was taken up in Et_2O and filtered to remove an insoluble solid. The filtrate was washed with dilute aqueous NaOH, cold H_2O, dilute aqueous HCl, cold H_2O, and saturated brine and dried. After filtration, the Et_2O solution was concentrated to dryness in vacuo to give a yellow-brown oil. Distillation of the crude product gave a colorless oil (10.2 g, 66%); bp 87–89 °C (17 mm); ^1H NMR δ 2.25 (6 H, d), 7.0–7.2 (2 H, m). Anal. (C_8H_8BrF), C, H.

Resolution of 100 and 110. The resolution of lactones **100** and **110** was accomplished according to the procedure described in ref 1. The physical properties of their corresponding diastereomeric amides are listed below and those of the enantiomeric lactones formed after basic hydrolysis and relactonization are listed in Table III (**100(+)** and **100(−)**, **110(+)** and **100(−)**).

(*S*)-α-Methylbenzylamides of 100. Elution on Waters Prep LC500 with CH_2Cl_2–MeOH (85:15, v/v) provided the 3*R*,5*S* isomer (the absolute configuration was determined on the resultant lactone, **100(+)**, by X-ray crystallographic analysis) in 42% yield (84% yield assuming an equal distribution of the enantiomeric lactones), mp 127–128.5 °C, >94% pure by HPLC. HPLC data: elution times were 4.0 min for the 3*S* isomer and 4.5 min for the 3*R* isomer (CH_2Cl_2–MeOH (98:2, v/v)), 2 mL/min on a μ Porasil column. An analytical sample was prepared by trituration with Et_2O, mp 128–129 °C. Anal. ($C_{27}H_{26}Cl_2FNO_3$) C, H, N.

The diastereomeric 3*S*,5*R* amide was not purified further (>95% by HPLC) but was converted to the lactone (**100(−)**).

(*S*)-α-Methylbenzylamides of 110. The amides were treated as above. **Amide I**: 33% yield, mp 110–112 °C, >95% by HPLC and gives rise to **110(−)**. HPLC data: elution time = 2.31 min (hexane–*i*-PrOH (91.5:8.5, v/v)), 4 mL/min on a DuPont silica column. An analytical sample was prepared by crystallization from Et_2O–hexane, mp 113–115 °C. Anal. ($C_{30}H_{34}FNO_3$) C, H, N.

Amide II: 27% yield, mp 86–89 °C, >99% by HPLC and gives rise to **110(+)**. Elution time = 3.16 min. An analytical sample was prepared by crystallization from Et_2O–hexane, mp 87–89 °C. Anal. ($C_{30}H_{34}FNO_3$) C, H, N.

X-ray Structure Analysis. The single-crystal analysis of structure **100(+)** was carried out on a fully automated Enraf-Nonius CAD4 diffractometer using graphite monochromated Cu Ka radiation (1.5418 Å) in the $2\theta/\omega$ scan mode to a maximum 2θ of 115°. The unit cell dimensions of a specimen grown in ether are a = 6.746 (2) Å, b = 8.781 (5) Å, c = 15.213 (5) Å, α = 83.95 (3)°, β = 89.79 (2)°, γ = 99.20 (3)°, V = 884 (1) Å^3, and D_{calcd} = 1.428 g/cm^3 e in the acentric space group $P\bar{1}$ (Z = 2). Of the 2432 unique reflections, 2057 (84.6%) were considered observeds at the level $I \geq 3\sigma(I)$. Corrections for absorption, Lorentz and polarization factors were made to the raw data. Data reduction, least-squares refinement, and other related crystallographic calculations were carried out with the SDP[19] set of computer programs running on a PDP 11/60 computer.

A trial structure was obtained by the direct methods computer program MULTAN.[20] Missing non-hydrogen atoms were located by difference electron density syntheses. All non-hydrogen atoms were refined by full-matrix least-squares using anisotropic temperature factors. After suitable refinement, idealized hydrogen atoms were added using isotropic temperature factors of the atoms to which they were bonded. Only the positional parameters of hydrogen atoms were refined. The function minimized during least squares was $\sum w(|F_o| - |F_c|)^2$. The final unweighted residual index ($\sum||F_o| - |F_c||/\sum|F_o|$) was 0.04291.

The two formula units in the unit cell are related to one another by a pseudocenter of symmetry broken only by the chiral centers (C6/C6' and C4/C4') in the lactone ring. Because of this non crystallographic symmetry and the resultant correlation between pairs of atoms, it was necessary to refine each formula unit separately.

The absolute configuration was determined by the use of anomalous dispersion[21] as observed by intensity measurements on a selected series of reflections and their Friedel pairs. Selection of the correct enantiomer was corrobated by the use of Hamilton's[22] R factor ratio test. The ratio of R factors (R) was 0.0618/0.0598 = 1.033. The R factors were obtained from least-squares refinement of all non-hydrogen atoms to a minimum using no anomalous scattering terms followed by calculation of structure factors using appropriate anomalous scattering terms with a change in sign of $\Delta f''$ in one case to simulate an enantiomeric coordinate system. The significance point of R (1, 1606, 0.005) was calculated to be 1.0025 from a total of 451 parameters, 2057 reflections (1606 degrees of freedom) at the 0.005 level of significance. Therefore, at the 0.5% level, we can reject the hypothesis that the data giving the higher R factor describes the correct enantiomer.

The atomic numbering scheme coincides exactly with the ORTEP[23] drawing of Figure 1. The two formula units in the asymmetric unit have identical numbering schemes with the addition of a prime (') on one molecule to distinguish it from the other. Hydrogens are labeled according to the atom to which it was bonded with suffixes of either "A", "B" or "C" when more than one hydrogen atom shares a heavier atom.

HMG-CoA Reductase Inhibition Assay. IC_{50} values were determined by plotting percentage inhibition against test compound concentration (four or five levels) and fitting a straight line to the resulting data by using the least-squares method. See part 1 for a full description of protocol.

Acknowledgment. We extend our thanks to Drs. E.

(19) Okaya, Y.; Frenz, B.; Brice, M.; Corfield, P.; Hodgson, K.; Rohrer, D.; Sinn, E., Enraf-Nonius Structure Determination Package, Revision 3-5; April 1980, An Integrated Set of Crystallographic Computer Programs Writtem for Use on PDP-11 Series of Computers.
(20) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M., "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data"; Universities of York, England and Louvain, Belgium, 1978.
(21) Bijvoet, J. M.; Peeredeman, A. F.; Van Bommel, A. J. *Nature (London)* **1951**, *168*, 271.
(22) Hamilton, W. C. *Acta Crystallogr.* **1965**, *15*, 502.
(23) Johnson, C. K., 1965. ORTEP. Report ORNL-3794, Oak Ridge National Laboratory, TN.

H. Cordes and R. F. Hirschmann for their encouragement during the course of this study, to Dr. T. Verhoeven for the preparation of nitrile 12, to Dr. W. C. Randall and J. P. Moreau for analytical support, to Dr. D. W. Cochran and J. S. Murphy for the ^1H NMR spectra, and to M. Z. Banker for manuscript preparation.

Supplementary Material Available: ^1H NMR data for biphenylcarboxaldehydes 3 and 3-biphenylylpropenals 4 plus atomic parameters for 100(+) (8 pages). Ordering information is given on any current masthead page.

Synthesis and Investigation of the β-Adrenoceptor Agonist and Platelet Antiaggregatory Properties of 1,7,8-Trisubstituted 2,3,4,5-Tetrahydro-1*H*-2-benzazepine Analogues of Trimetoquinol

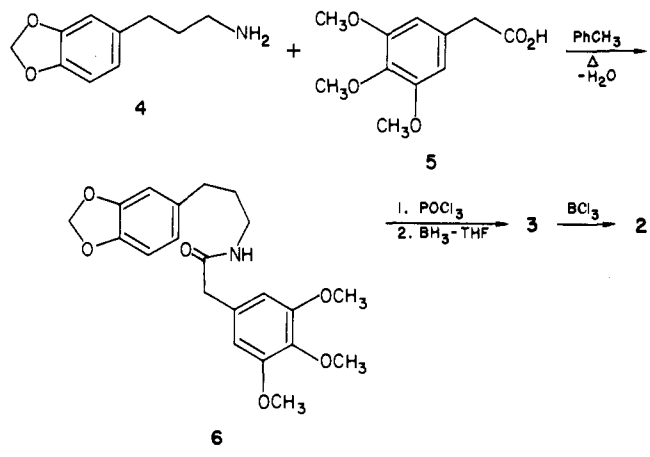
Michael T. Clark, Jane Chang, Stephen S. Navran, Huzoor-Akbar, Asoke Mukhopadhyay, Hebatalla Amin, Dennis R. Feller, and Duane D. Miller*

Divisions of Medicinal Chemistry and Pharmacognosy and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210. *Received May 15, 1985*

The synthesis and biological evaluation of 7,8-dihydroxy (2) and 7,8-methylenedioxy (3) analogues of 1-[(3,4,5-trimethoxyphenyl)methyl]-2,3,4,5-tetrahydro-1*H*-2-benzazepine on β-adrenoceptor systems and human platelets were undertaken and compared with trimetoquinol (TMQ, 1). Whereas 1 is a potent β-adrenoceptor agonist in guinea pig atria and trachea (pD_2 = 8.2), analogue 2 was marginally effective at relaxing guinea pig tracheal smooth muscle (pD_2 = 4.4) and inactive as an agonist on guinea pig atria. Analogues 2 and 3 were inhibitors of phospholipase C (PLC; from *Clostridium perfringens*) induced and secondary wave of ADP-induced aggregation responses and inactive against low-dose thrombin-induced or stable endoperoxide (U46619) induced human platelet aggregation. Against ADP-induced serotonin secretion, 3 was 9-fold more active than analogue 2. Further, the rank order of TMQ isomers and 3 as inhibitors of PLC-induced platelet aggregation, serotonin secretion, and phosphatidylinositol degradation was identical (3 > (*S*)-(−)-1 > (*R*)-(+)-1). The results suggest that these compounds are blocking the action of PLC by interfering with phosphatidylinositol turnover in platelet membranes. The inhibition of ADP-induced responses in human platelets by analogues 2 and 3 also suggests a site of inhibition at a level of arachidonic acid release. Thus, ring expansion of 1 as in the benzazepine analogues 2 and 3 has allowed us to develop selective inhibitors of platelet function that lack significant β-adrenoceptor activity.

Trimetoquinol (1) is a potent β-adrenoceptor agonist[1,2] and platelet antiaggregatory drug.[3,4] Our laboratory has investigated the effect of structural modification of 1 with the goal of obtaining highly selective β_2-adrenergic agonists and antiplatelet agents.[5-10] To our knowledge, no investigation, other than our own, has been carried our to establish the effect of enlargement of the tetrahydroisoquinoline ring to a tetrahydro-1*H*-2-benzazepine on β-adrenergic activity. Recently, we have reported[11] that 2 and 3 were found to be more potent than 1 as inhibitors of bacterial phospholipase C (PLC) induced human platelet aggregation. In the following discussion, the synthesis and more extensive biological evaluation of 2 and 3 in human platelets and of 2 in β_1- and β_2-adrenergic systems is reported.

Scheme I



Chemistry. The synthesis of compound 2 involved the preparation of *N*-[[3,4-(methylenedioxy)phenyl]propyl]-3,4,5-trimethoxyphenylacetamide (6) from 3-[3,4-(methylenedioxy)phenyl]-1-aminopropane (4) and 3,4,5-trimethoxyphenylacetic acid (5). Compound 6 was then cyclized via a Bischler–Napieralski ring closure and converted to 2 with BCl_3 as illustrated in Scheme I.

Of importance in the synthetic strategy was the preparation of compound 4. The original preparation of 4 involved reduction, via hydrogenation or sodium amalgam, of 3,4-(methylenedioxy)cinnamic acid to 3-[3,4-(methylenedioxy)phenyl]-1-propionic acid.[12] The propionic acid

(1) Iwasawa, Y.; Kiyomoto, A. *Jpn. J. Pharmacol.* **1967**, *17*, 143-152.
(2) Feller, D. R.; Venkatraman, R.; Miller, D. D. *Biochem. Pharmacol.* **1975**, *24*, 1357-1359.
(3) Shtacher, G.; Crowley, H. J.; Dalton, C. *Biochem. Pharmacol.* **1976**, *25*, 1045-1050.
(4) Mayo, J. R.; Navran, S. S.; Huzoor-Akbar; Miller, D. D.; Feller, D. R. *Biochem. Pharmacol.* **1981**, *30*, 2237-2241.
(5) Miller, D. D.; Kador, P. F.; Venkatraman, R.; Feller, D. R. *J. Med. Chem.* **1976**, *19*, 763-766.
(6) Osei-Gyimah, P.; Piascik, M. T.; Fowble, J. W.; Feller, D. R.; Miller, D. D. *J. Med. Chem.* **1978**, *21*, 1173-1178.
(7) Piascik, M. T.; Osei-Gyimah, P.; Miller, D. D.; Feller, D. R. *Biochem. Pharmacol.* **1979**, *28*, 1807-1810.
(8) Mukhopadhyay, A.; Sober, D. J.; Chang, J.; Slenn, R. T.; Amin, H. M.; Miller, D. D.; Feller, D. R. *Eur. J. Pharmacol.* **1982**, *77*, 209-219.
(9) Sober, D. J.; Chang, J.; Fowble, J. W.; Mukhopadhyay, A.; Feller, D. R.; Miller, D. D. *J. Med. Chem.* **1981**, *24*, 970-974.
(10) Mukhopadhyay, A.; Navran, S. S.; Amin, H. M.; Abdel-Aziz, S. A.; Chang, J.; Sober, D. J.; Miller, D. D.; Feller, D. R. *J. Pharmacol. Exp. Ther.* **1985**, *232*, 1-9.
(11) Navran, S. S.; Romstedt, K.; Chang, J.; Miller, D. D.; Feller, D. R. *Thromb. Res.* **1984**, *33*, 499-510.
(12) Haworth, W. N.; Perkin, W. H., Jr.; Robinson, R. *J. Chem. Soc.* **1907**, *91*, 1087.

0022-2623/86/1829-0181$01.50/0