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

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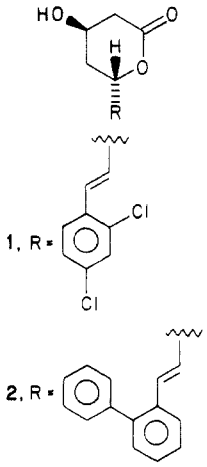
The syntheses of a series of 7-(3,5-disubstituted [1,1'-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acids and their lactones are reported. Intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitory activity is enhanced markedly when the biphenyl moiety is substituted by chloro or methyl groups 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.

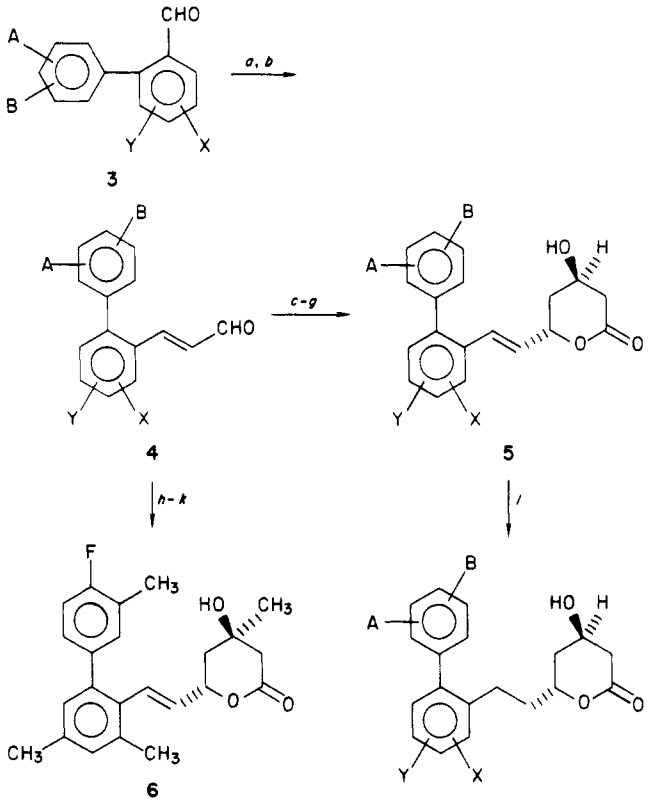
We previously reported on a series of 3,5-dihydroxypentanoic acids, their δ lactones, and other derivatives which were shown to possess varying degrees of intrinsic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity.[1] The most potent inhibitor bearing a monocyclic substituent 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

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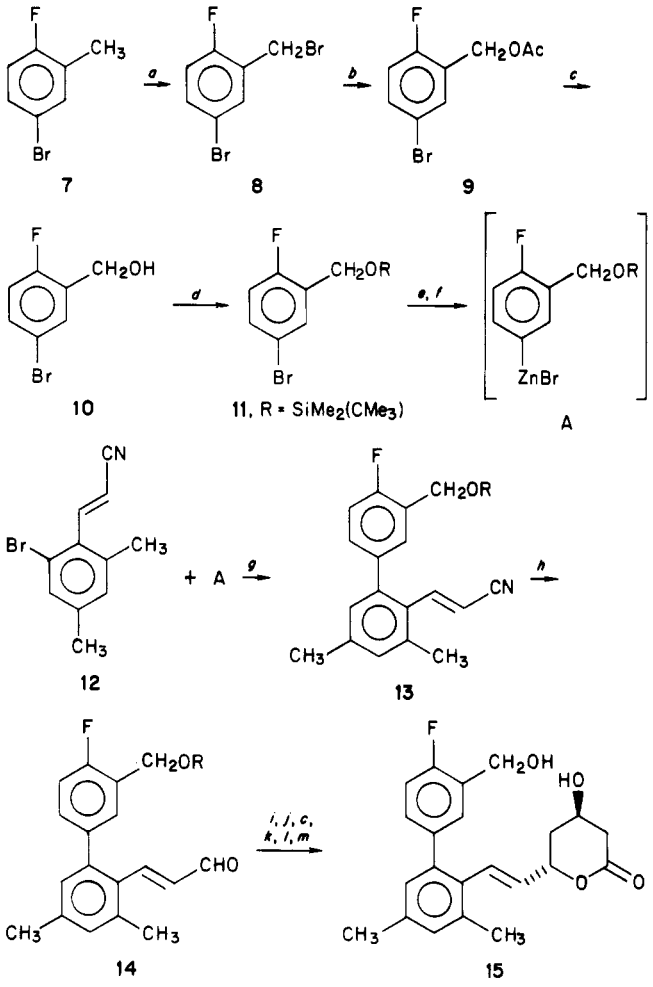
(1) Stokker, G. E.; Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.
(2) Hoffman, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Evans, B. E.; Gilfillan,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

Scheme II

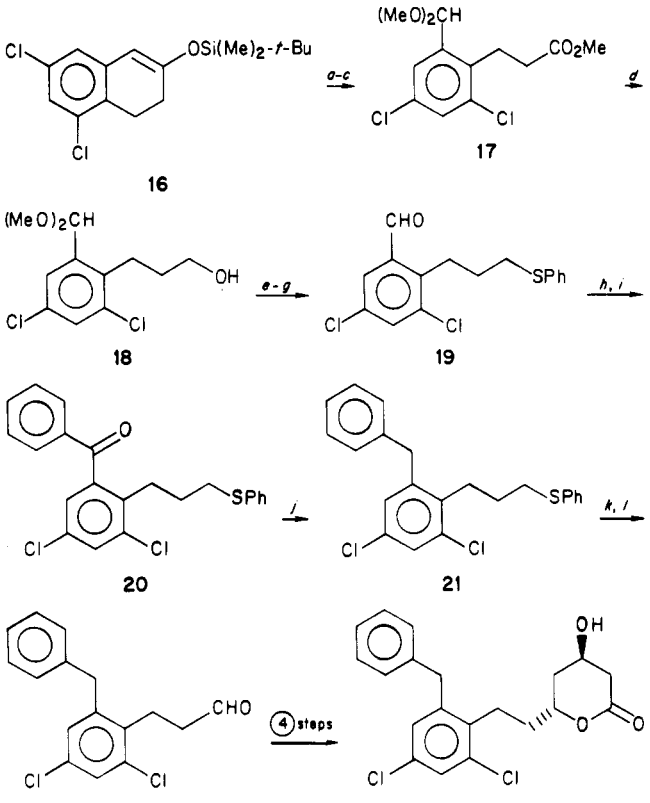


[a] Br_2, $h\nu$. [b] NaOAc, Δ. [c] OH^-. [d] $ClSi(CH_3)_2C(CH_3)_3$. [e] Mg. [f] $ZnBr_2$. [g] $Ni(Ph_3P)_2Cl_2$. [h] Dibal. [i] $^-CH_2CO^-CHCO_2CH_3$. [j] Et_3B, $NaBH_4$, −98 °C. [k] H^+. [l] $C_6H_5CH_3$, Δ. [m] $(n\text{-}C_4H_9)_4NF$.

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

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+}.

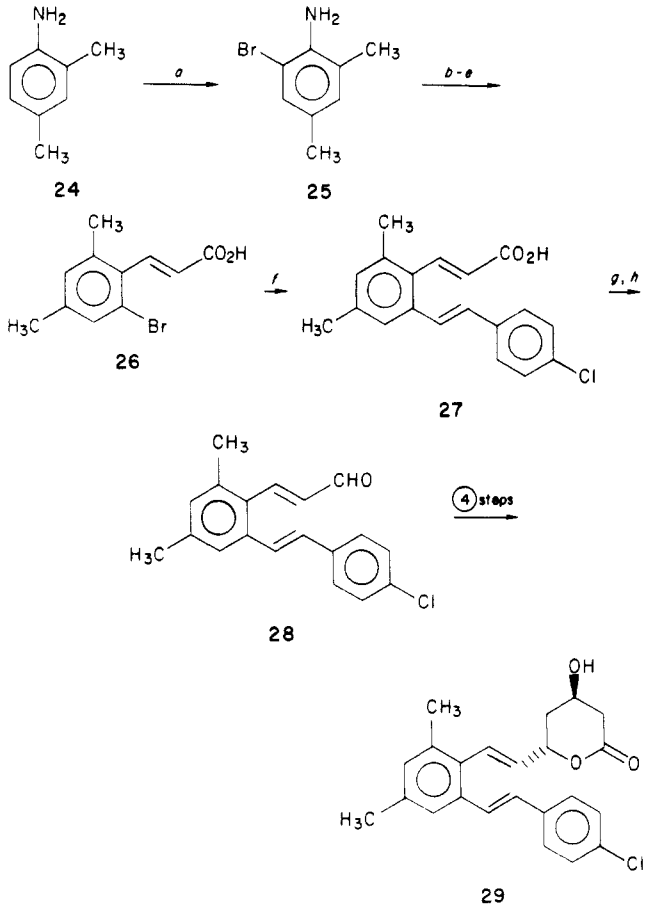
four-step sequence **7** → **8** → **9** → **10** → **11**, using the reagents indicated in Scheme II. Grignard formation followed by transmetalation with anhydrous zinc bromide provided arylzinc bromide A, which was immediately coupled with cinnamyl nitrile **12** catalyzed by bis(triphenylphosphine)nickel 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.

Scheme IV

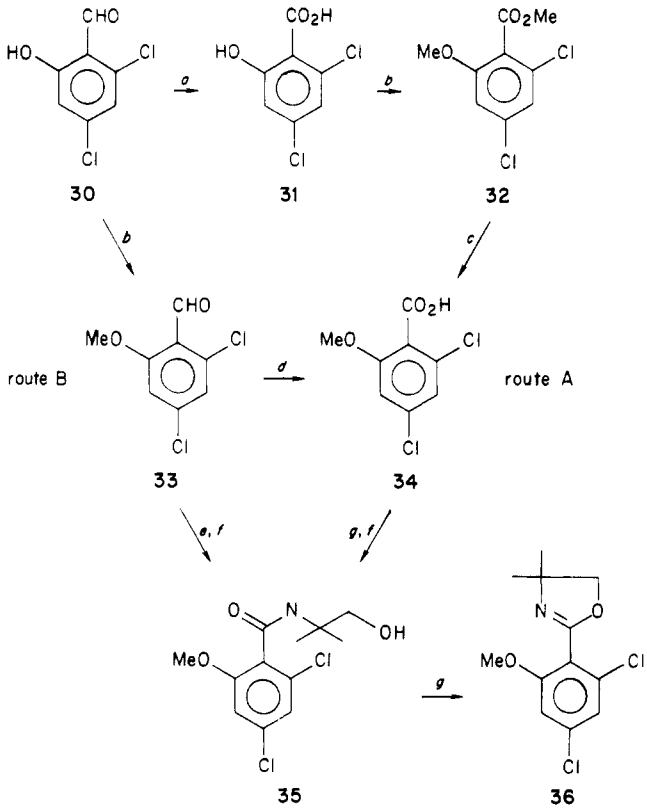


[a] Br_2. [b] HONO. [c] $CH_2{=}CHCO_2Et$. [d] OH^-, Δ. [e] $H_3{}^+O$. [f] 4-Cl-$C_6H_4CH{=}CH_2$, $(C_6H_5)_3P$, $Pd(OAc)_2$, 1 mol %, Et_3N, Δ. [g] $SOCl_2$. [h] $((C_6H_5)_3P)_2CuBH_4$, $(C_6H_5)_3P$.

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.

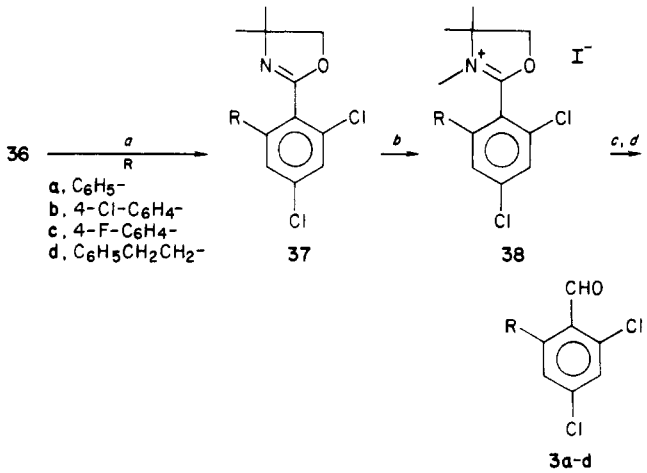
Route B, the more expeditious of the two routes, was based on the key conversion of **33** → **35** via radical bromination/oxidation and subsequent amination.[11] The oxidation of **33** → **34** with "purple benzene", essentially

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, $h\nu$. [f] $H_2NC(CH_3)_2CH_2OH$. [g] $SOCl_2$.

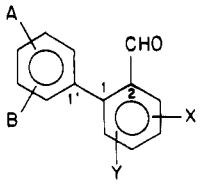
Scheme VI. Method 1



[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

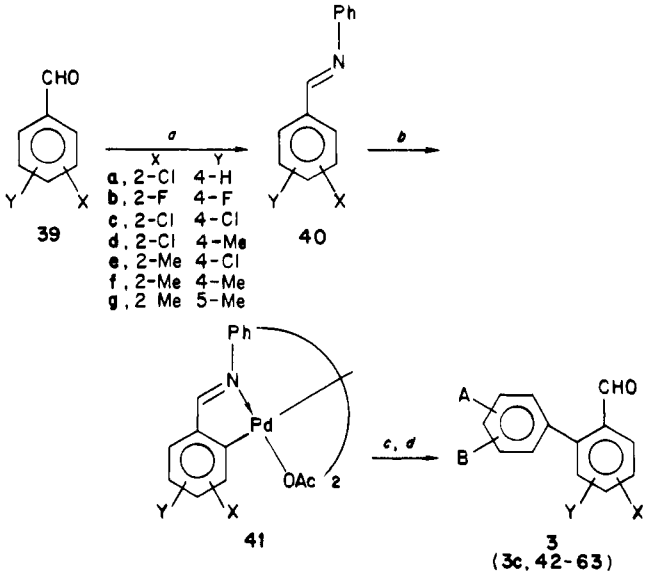
Table I. Physical Properties of Biphenylcarboxaldehydes 3[a]



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



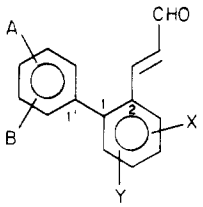
[a] $H_2NC_6H_5$. [b] $Pd(OAc)_2$. [c] ABC_6H_3MgX, 4 equiv of Ph_3P. [d] H_3^+O.

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

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

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

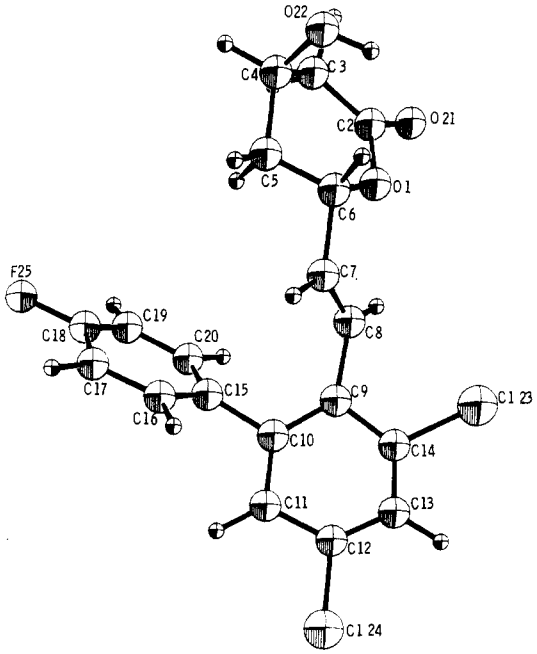


Figure 1. Computer-generated ORTEP drawing of one formula unit of structure **100**(+) within the unit cell.

ition was beneficial (i.e., Cl in **98** or F in **100**). A methyl in the 2′-position was also contraindicated (**92** vs. **90**, **105**

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