Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 3.[1,2] Lactones of 6-Phenoxy-3,5-dihydroxyhexanoic Acids

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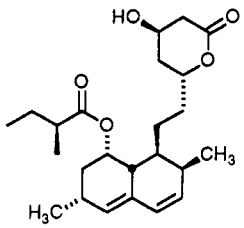
A group of 43 optically active sodium carboxylates (**11a-qq** and the corresponding lactones **4** were prepared from respective phenols **8** according to Schemes I-III. Phenols **8** were synthesized from commercially available compounds according to Schemes IV-IX. A number of these HMG-CoA reductase inhibitors **11** exceeded mevinolin's activity in vitro (Tables II and III). Selected lactones **4** effectively inhibited hepatic "de novo" cholesterol synthesis in rats in vivo (Table IV). After po administration to rabbits, **4ff(11ff)**, **4hh**, and notably **11jj** reduced plasma cholesterol levels more potently than mevinolin (**1**) (Table V). Whereas **4ff(11ff)** displayed the slight superiority expected according to in vitro data, **4hh** and **11jj** were considerably more potent than expected. Each of these compounds had only moderate activity after po administration to dogs (Table VI). Compound di-**11ii**, a hybrid of the structural elements of probucol (**60**) and HMG-CoA reductase inhibitors, after po administration to rats decreased serum lipoproteins and increased HDL/LDL ratio better than probucol (Table VII). HMG-CoA reductase inhibitor **11ll** and phenolic building blocks **8**, notably **8jj** and **8kk**, inhibited LDL oxidation in vitro (Table VIII). Chemical structure-activity relationships (Table IX) and the pharmacological profile of phenoxy-type inhibitors **11** diverged from those of known HMG-CoA reductase inhibitors.

The fungal metabolite mevinolin (**1**) is a potent inhibitor of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase)[3] and lowers plasma cholesterol levels in man,[4] thus diminishing the risk of coronary heart disease.[5]



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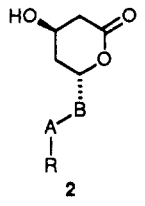

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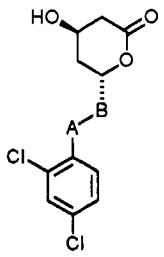

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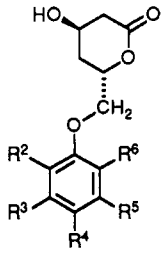

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A plethora of work has been directed toward the preparation of synthetic analogues **2**. In **2** (A-B = CH_2CH_2 or CH=CH), the stereochemically complex hexahydronaphthalene moiety of **1** has been replaced by suitably substituted, achiral, aromatic moieties R^{6-16} and open-chain moieties R.[17,18] Compounds **2** that exceeded the activity of mevinolin (**1**) in vitro and in vivo have been described.[1,2,9,10,11,19]

Comparatively little effort has been directed toward the modification of the "bridging-unit" A-B of analogues **2**. This may be due to an early report of Stokker et al.[6a] that discouraged this modification. From these data it was concluded[6a] that replacement of the *trans*-ethenyl bridge with the ethinyl and oxymethylene groups resulted in loss of activity. However it should be noticed that these data were limited and that **3** might be an unsuitable model compound, due to its low affinity to the active site of the enzyme.[20] This assumption was confirmed, when we obtained highly efficacious compounds of type **2** bearing an ethinyl bridge (A-B = C≡C, $IC_{50} \leq 10$ nM).[21]

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(1) Part 1 of this series: Beck, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Krause, R.; Paulus, E.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 52.
(2) Part 2 of this series: Jendralla, H.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Schubert, W.; Wess, G. *J. Med. Chem.* **1990**, *33*, 61.
(3) Hoffman, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849.
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(5) LRC-CPPT *J. Am. Med. Assoc.* **1984**, *251*, 351 and 365.
(6) (a) 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. (b) 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.* **1986**, *29*, 159. (c) Stokker, G. E.; Alberts, A. W.; Anderson, P. S.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Hirshfield, J.; Holtz, W. J.; Hoffman, W. F.; Huff, J. W.; Lee, T. J.; Novello, F. C.; Prugh, J. D.; Rooney, C. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 170.
(7) Stokker, G. E.; Alberts, A. W.; Gilfillan, J. L.; Huff, J. W.; Smith, R. L. *J. Med. Chem.* **1986**, *29*, 852.
(8) Sandoz, patent WO 84/02131, 1984.
(9) Sandoz, patent WO 86/00307, 1986.
(10) Sandoz, patent WO 86/07054, 1986.
(11) Sandoz, European Application EP-A-0221025, 1987.
(12) Sandoz, European Application EP-A-0265640, 1988.
(13) Hoechst, European Application EP-A-0324347, 1989.
(14) Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 21.
(15) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758.
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(17) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; von Kerekjarto, B.; Krause, R. *Tetrahedron Lett.* **1988**, *29*, 929.
(18) Bristol-Myers, Deutsche Offenlegungsschrift DE 3805801, 1988.
(19) Bayer, European Application EP-A-0325130, 1989.
(20) The potency of **3** (A-B = (*E*)-CH=CH and OCH_2) is about 10^{-3} and 10^{-4}, respectively, compared with the most active compounds in the present report.

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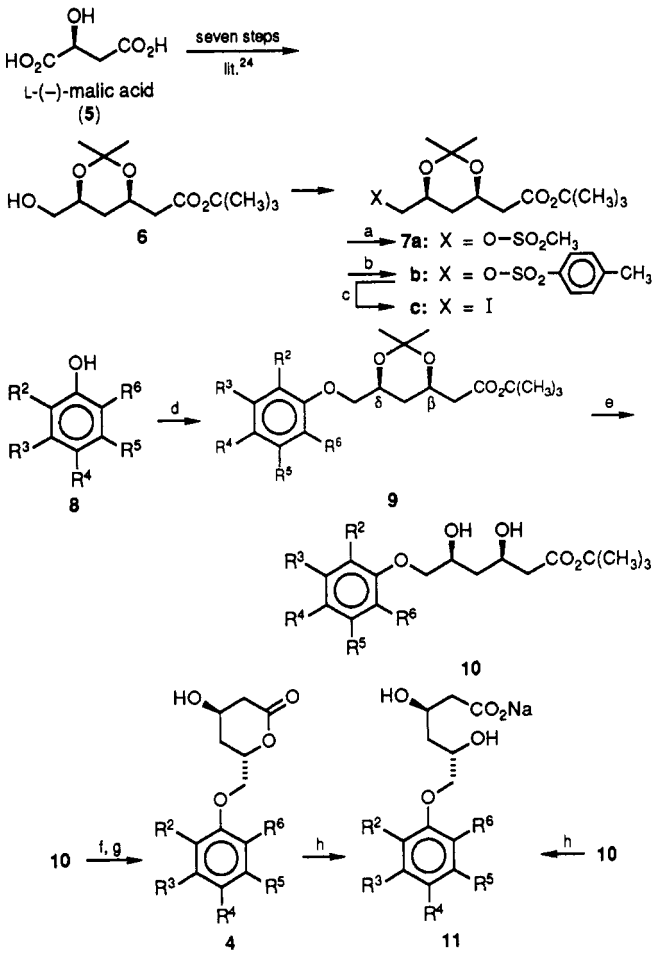
Scheme I.[a] Preferred Synthesis of Optically Pure HMG-CoA Reductase Inhibitors 4 ("Chiral Pool" Approach Based on L-(−)-Malic Acid)



[a] (a) CH_3SO_2Cl/pyridine/0 °C; (b) $CH_3C_6H_4SO_2Cl$/pyridine/0 °C; (c) NaI, acetone, reflux; (d) **7a**/K_2CO_3/DMSO/60–90 °C; (e) 2 N HCl/EtOH/THF/25 °C; (f) CF_3CO_2H/25 °C; (g) $NaHCO_3$/Na_2CO_3 → pH 7; (h) 1 N NaOH/EtOH/25 °C.

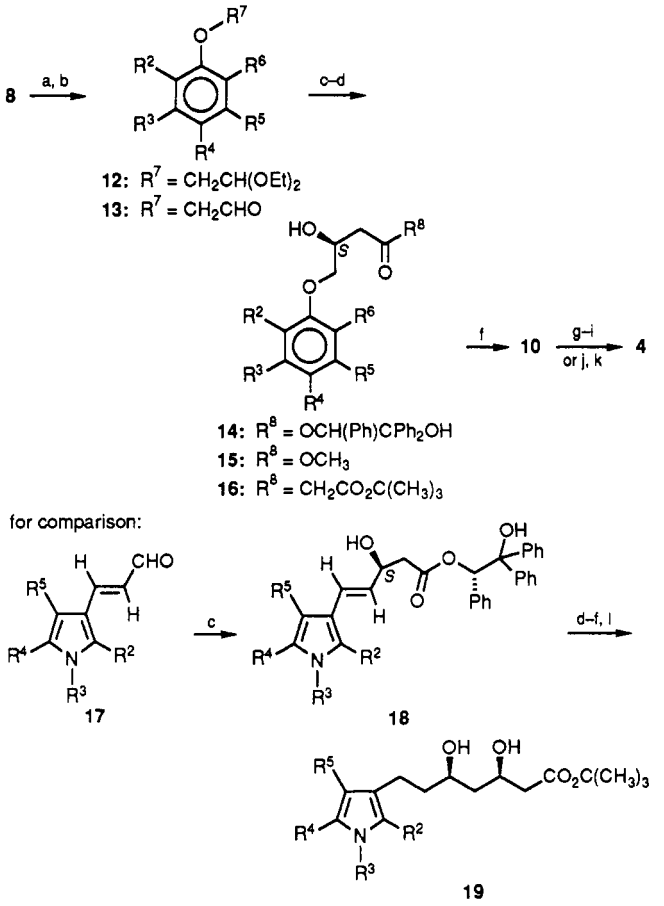
In this paper we will report phenoxy-type inhibitors **4**. Some compounds analogous to **4**, based on β-quinolinols, β-naphthols, and thiophenols, are reported for comparison.

Thiophenoxy analogues (**2**: A–B = SCH_2) were briefly investigated. In the few cases studied, they were found to be slightly less active than identically substituted phenoxy analogues **4**.[22,23]

Chemistry

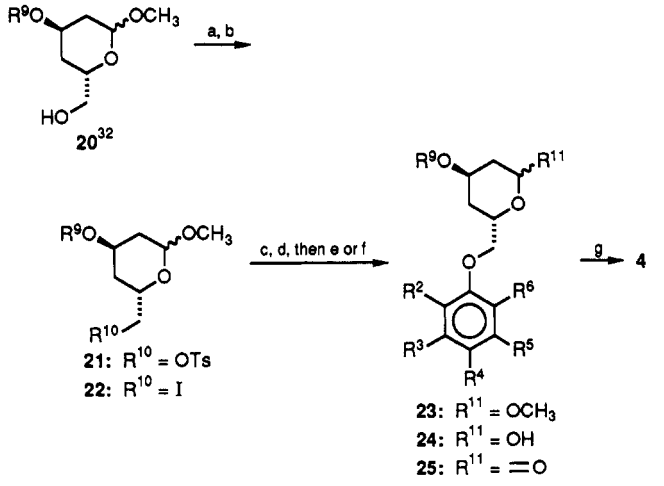
The β-hydroxy lactones **4** and their corresponding β,δ-dihydroxy sodium carboxylates **11** were prepared from phenols **8** according to Schemes I–III. The "chiral pool" approach, as depicted in Scheme I, is the preferred mode of synthesis. The diastereomerically and optically pure synthon **6** was conveniently prepared in seven steps from commercially available, inexpensive L-(−)-malic acid (**5**).[24]

Scheme II.[a] Synthesis of Optically Enriched HMG-CoA Reductase Inhibitors 4 via Asymmetric Aldol Addition



[a] (a) $BrCH_2CH(OEt)_2/K_2CO_3$/DMSO/90 °C; (b) 2 N HCl/acetone/65 °C; (c) LDA/(*S*)-(−)-$CH_3CO_2CH(Ph)CPh_2OH$[28]/THF/−90 °C; (d) $NaOCH_3/CH_3OH$/25 °C; (e) $CH_3CO_2C(CH_3)_3$/LDA/−70 °C → −20 °C; (f) $Et_3B/CH_3OH/NaBH_4$/−80 °C; (g) 1 N NaOH/EtOH/25 °C; (h) HCl/H_2O; (i) $NEt_3/ClCO_2Et$/THF/−5 °C; (j) CF_3CO_2H/25 °C; (k) $NaHCO_3/Na_2CO_3$ → pH 7; (l) Pd/C/H_2.

Scheme III[a,b] Alternative Synthesis of Optically Pure HMG-CoA Reductase Inhibitors 4 ("Chiral Pool" Approach Based on α-D-(+)-Glucose; R^9 = *t*-$BuPh_2Si$)



[a] (a) p-$CH_3C_6H_4SO_2Cl$/pyridine/CH_2Cl_2/5 °C; (b) NaI/acetone/reflux; (c) **8**[b]/K_2CO_3/DMSO/60 °C; (d) CH_3CO_2H/H_2O/THF/reflux; (e) CrO_3/pyridine/CH_2Cl_2/25 °C; (f) *N*-iodosuccinimide (NIS)/(*n*-Bu)$_4$NI/CH_2Cl_2/25 °C; (g) (n-Bu)$_4$NF/CH_3CO_2H/THF/20 °C. [b] β-Naphthols **8dd,ee**, β-quinolinols **8mm-oo**, and thiophenol **8pp** were reacted according to the same scheme.[33]

(21) Hoechst, European Application EP-A-0361273, 1990.
(22) (a) Hoechst, Deutsche Offenlegungsschrift DE 3632893, 1988. (b) Hoechst, Deutsche Offenlegungsschrift DE 3929913, 1990.
(23) Inhibitors **2** with a fluoroethenyl bridge (**2**: A–B = FC=CH) were more potent than their unfluorinated analogues (A–B = HC=CH). Baader, E.; Bartmann, W.; Beck, G.; Below, P.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G. *Tetrahedron Lett.* **1989**, *30*, 5115.
(24) Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, *31*, 2545.

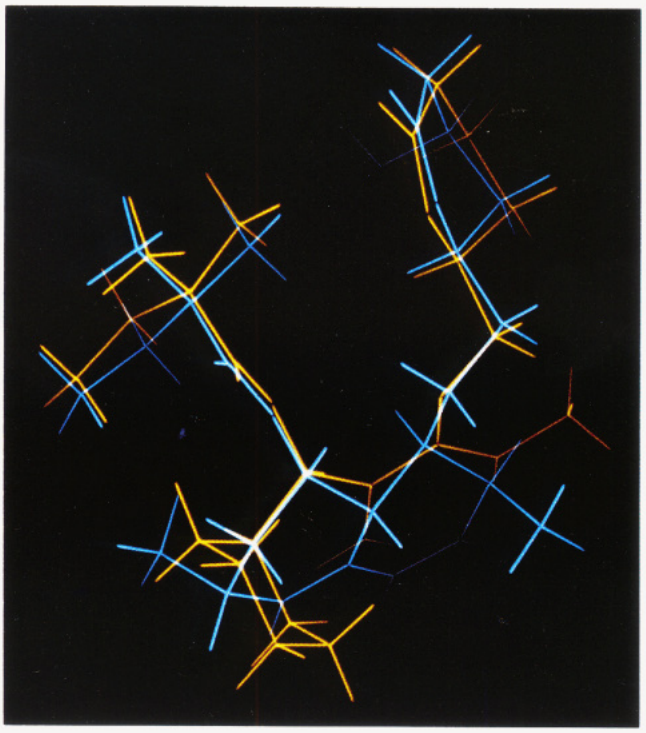
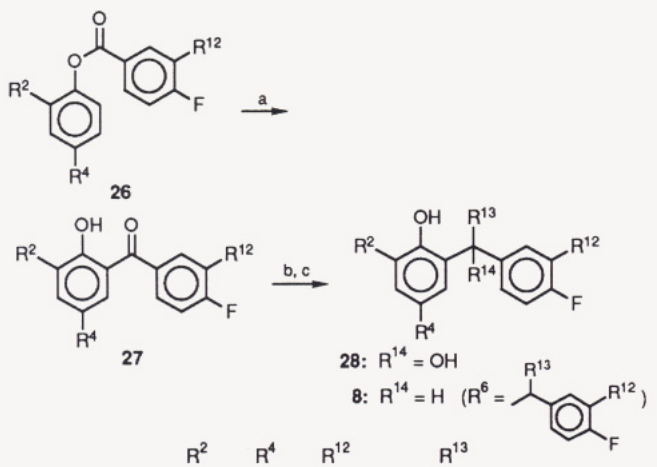


Figure 1. Superposition of synvinolin and compound **4r**.

Scheme IV.[a] Synthesis of Phenols **8a–i**

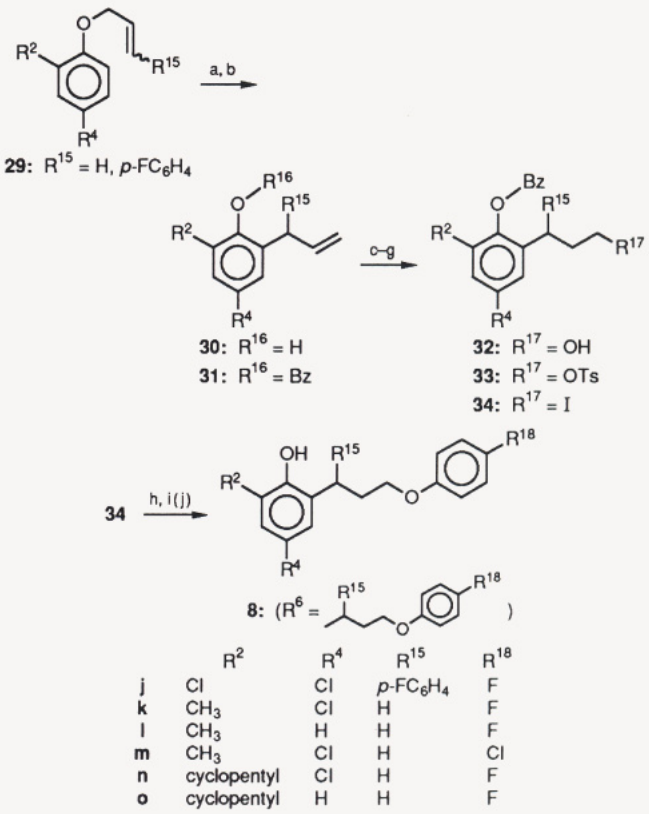


	R^2	R^4	R^{12}	R^{13}
a	CH_3	CH_3	H	*p*-FC_6H_4
b	Cl	Cl	H	*p*-FC_6H_4
c	CH_3	Cl	H	*p*-FC_6H_4
d	CH_3	CH_3	H	*p*-$CH_3OC_6H_4$
e	CH_3	CH_3	H	*m*-$CF_3C_6H_4$
f	CH_3	CH_3	H	CH_3
g	CH_3	CH_3	H	*i*-Bu
h	Cl	CH_3	CH_3	*m*-CH_3-*p*-FC_6H_3
i	Cl	Cl	CH_3	*m*-CH_3-*p*-FC_6H_3

[a] (a) $AlCl_3$/~150 °C; (b) R^{13}–Br/Mg/THF; (c) Pd/C/H_2/AcOH/(concentrated HCl)/25 °C.

Ester **6** was supplied with several different leaving groups to give mesylate **7a**, tosylate **7b**, iodide **7c**, and the unstable triflate **7d**. Of these compounds, only mesylate **7a** proved to be suitable for a clean, stereochemically homogeneous coupling reaction with phenols **8** to give **9** in 75–90% yield.[25] Cleavage of the acetonide protecting group followed by a combined cleavage of the *tert*-butyl ester and lactonization gave the diastereomerically and optically pure lactones **4** in 60–75% overall yield based on phenols **8**.

Scheme V.[a] Synthesis of Phenols **8j–o**



	R^2	R^4	R^{15}	R^{18}
j	Cl	Cl	*p*-FC_6H_4	F
k	CH_3	Cl	H	F
l	CH_3	H	H	F
m	CH_3	Cl	H	Cl
n	cyclopentyl	Cl	H	F
o	cyclopentyl	H	H	F

[a] (a) $C_6H_5N(CH_3)_2$/160 °C; (b) BzCl/K_2CO_3/DMF/75 °C; (c) 9-BBN/THF/25 °C → reflux; (d) EtOH/2 N NaOH/H_2O_2/25 °C → reflux; (e) SiO_2 chromatography; (f) TsCl/pyridine/25 °C; (g) NaI/acetone/reflux; (h) *p*-R^{18}-C_6H_4OH/K_2CO_3/DMSO/50 °C; (i) Pd/C/H_2/AcOH/EtOAc or concentrated HCl/25 °C/20 min; (j) Pd/C/H_2/EtOAc/12 h.

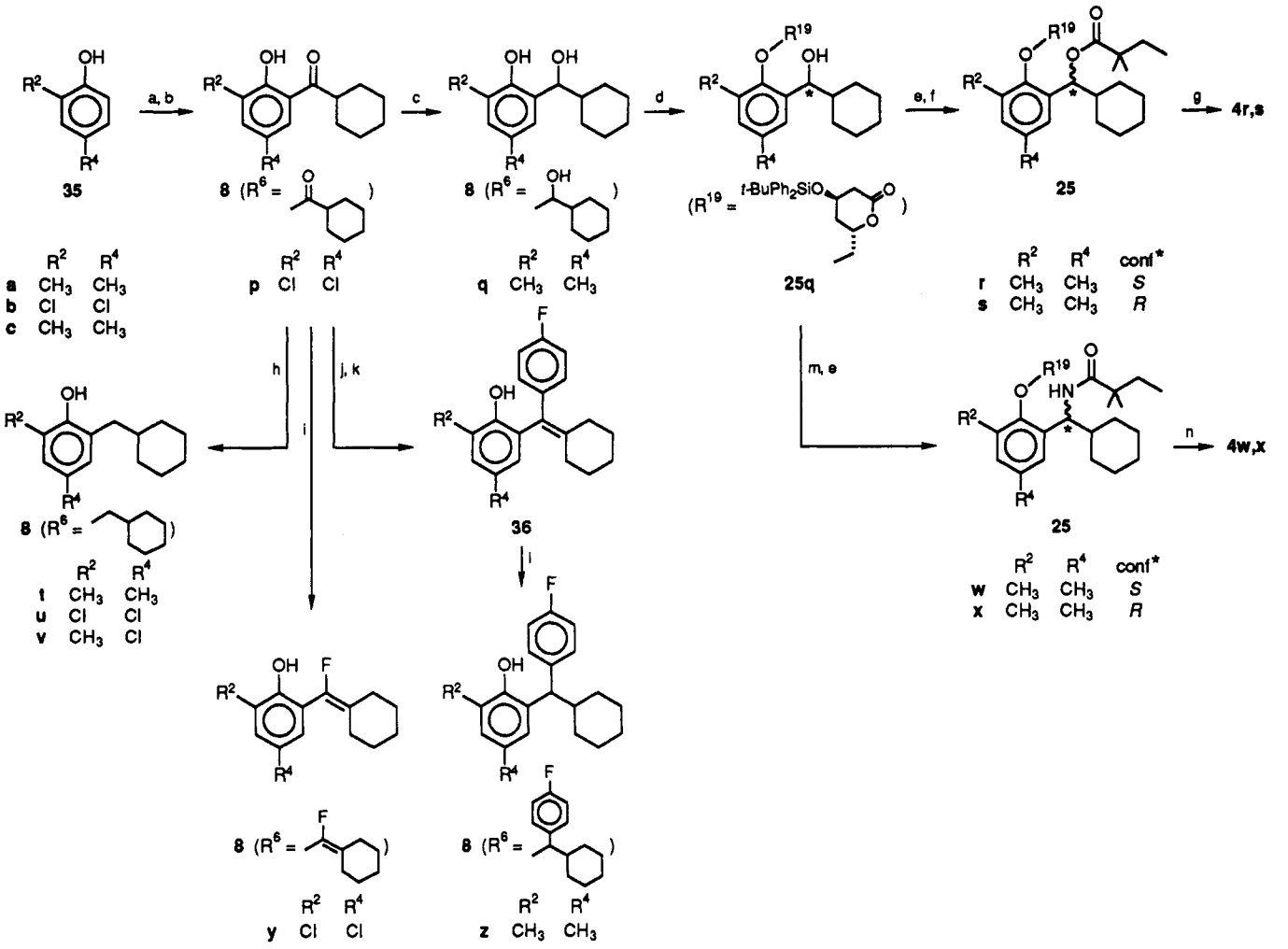
Scheme II summarizes the syntheses of optically enriched lactones **4** via asymmetric aldol addition[26,27] of the dianion generated from (*S*)-(−)-phenyl (2-hydroxy-2,2-diphenylethyl)acetate [(*S*)-(−)-HYTRA][28] and 2 equiv of LDA to substituted phenoxyacetaldehydes **13**.

We have shown recently that the addition of this dianion to 3-pyrrol-3-ylpropenals **17** proceeds with high asymmetric induction, leading to the β,δ-dihydroxyheptenoic esters **19** with optical purities of more than 92% ee.[2] Similar results were obtained in the addition of this dianion to chiral β-alkoxyaldehydes.[29] Therefore, we expected a similar degree of stereoselectivity for the addition of the dianion of HYTRA to α-phenoxyacetaldehydes **13**. However, the indicated 3(*S*)-hydroxy isomer **14** exceeded its undesired 3(*R*) diastereomer by only less than 82:18 (59–64% de, HPLC). The diastereomeric excess of **14** was not significantly improved by recrystallization, nor by a transmetalation of the lithium dianion of HYTRA with $MgBr_2$[27] and a lower reaction temperature[27] in the asymmetric aldol addition. The disappointing stereoselectivity was corroborated by analyses of methyl ester **15** [59–65% ee, HPLC on chiral column and ^1H NMR ($Eu(hfc)_3$) analyses]. Recrystallization of **15** did not significantly improve its optical purity.

(25) In the reaction of **7c** with phenol **8gg**, there was obtained 39% of **9** and 51% of a diastereomer besides 8% of unreacted **7c**. The 270-MHz ^1H NMR of the isolated diastereomer does not allow for an unequivocal decision between an isomerization at the β- or the δ-carbon atom.

(26) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.
(27) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397.
(28) Commercially available from Merck-Schuchardt, Germany.
(29) Mahler, U.; Devant, R.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035.

Scheme VI.[a] Synthesis of Phenols 8p–8z



[a] (a) $C_6H_{11}COCl/CH_2Cl_2/25$ °C; (b) $AlCl_3/150$ °C; (c) $NaBH_4/CH_3OH/H_2O/25$ °C; (d) three steps, Scheme III; (e) HPLC separation of the two diastereomers; (f) $(CH_3CH_2C(CH_3)_2CO)_2O$/toluene/DMAP/110 °C; (g) $(n\text{-}Bu)_4NF/CH_3CH_2C(CH_3)_2CO_2H$/THF/20 °C; (h) $LiAlH_4/AlCl_3/Et_2O$/reflux; (i) Et_2NSF_3/toluene/0 °C → 25 °C; (j) $p\text{-}FC_6H_4MgBr$/THF/0 → 25 °C; (k) 2 N HCl; (l) $Pd/C/H_2/CH_3OH$/25 °C; (m) 48% aqueous HF/$CH_3CH_2C(CH_3)_2CN$/25 °C/20–50 h; (n) $(n\text{-}Bu)_4NF$/AcOH/THF/25 °C.

Reaction of methyl ester **15** with 4 equiv of the enolate of *tert*-butyl acetate yielded *tert*-butyl β-keto-δ(*S*)-hydroxy carboxylate **16**. Highly stereoselective reduction of the keto group[30] was conducted with triethylborane and sodium borohydride to give *tert*-butyl β(*R*)-δ(*S*)-dihydroxy carboxylate **10**. Saponification of ester **10** with sodium hydroxide in ethanol/water gave sodium carboxylate **11**, which was converted to β-hydroxy lactone **4** via the mixed anhydride with ethyl chloroformate.

Alternatively, ester **10** can be transformed to β-hydroxy lactone **4** with trifluoroacetic acid (vide supra). The diastereomeric purity of **4** was >96.5% (HPLC), the ratio of enantiomers 81: 19 (62% ee, ^1H NMR/Eu(hfc)$_3$ analysis), in agreement with the optical purities of precursors **14** and **15** (vide supra). During the early phase of the investigation,[31] lactones **4** and sodium carboxylates **11** were prepared according to the chiral pool approach outlined in Scheme III. Alcohol **20**[32] was converted to the corresponding iodide **22** via tosylate **21**. Nucleophilic substitution of iodide **22** by the substituted phenol, β-naphthol, β-quinolinol, or thiophenol **8**[33] (K_2CO_3/DMSO) gave the protected lactol ether **23**, which was hydrolyzed to lactol **24**, and then oxidized to lactone **25**, and the silyl protecting group was removed to give β-hydroxy lactone **4**. Although this approach served to produce optically pure **4** with a wide variety of substituents R^2–R^6 in good yield, it cannot compete with the method depicted in Scheme I due to the lengthy synthesis (13 steps) of **22**.

Physical data and chemical yields of lactones **4** and corresponding sodium carboxylates **11** are collected in Table I. Additionally this table outlines which of the three procedures (Schemes I–III) was used to prepare **4** and **11** from the respective building block **8**. Lactone **4ff** was prepared according to all three procedures, allowing for a direct comparison of their efficiencies.

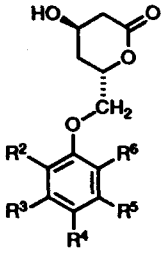
Substituted phenols, analogous β-naphthols, β-quinolinols, and thiophenols were synthesized as depicted in Schemes IV–IX.[33] Most of the synthetic steps correspond

(30) (a) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803. (b) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

(31) The first compounds **4** with potent in vitro and (partially) in vivo activity were prepared in 1985. Preliminary report: Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Jendralla, H.; von Kerekjarto, B.; Kesseler, K.; Krause, R.; Wess, G. International Symposium on Cholesterol Control and Cardiovascular Diseases: Prevention and Therapy, Milan, July 7–9, 1987, Abstract book, p 133.

(32) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Fehlhaber, H.-W.; Jendralla, H.; Kesseler, K.; Saric, R.; Schüssler, H.; Teetz, V.; Weber, M.; Wess, G. *Tetrahedron Lett.* **1988**, *21*, 2563.

Table I: Physical Properties and Yields of β-Hydroxy Lactones 4 and of Corresponding β,δ-Dihydroxy Sodium Carboxylates 11



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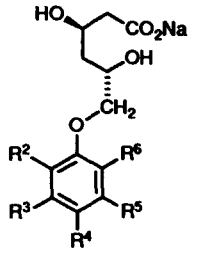


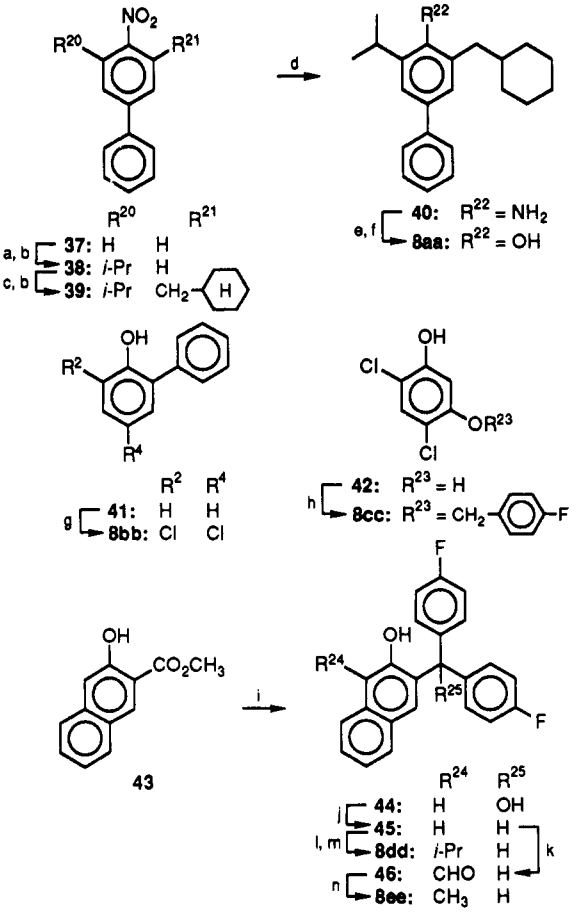
11

no.	R^2	R^3	R^4	R^5	R^6	mp,[a] °C	R_f (solvent)[b]	% yield[c] (procedure)[d]	formula[e]	no.[f]	dec, °C
4a	CH_3	H	CH_3	H	$CH(p\text{-}C_6H_4F)_2$	140–141[g]	0.19 (1)	73 (3)	$C_{27}H_{26}F_2O_4$	**11a**	*h*
4b	Cl	H	Cl	H	$CH(p\text{-}C_6H_4F)_2$	amorphous	0.20 (1)	84 (3)	$C_{25}H_{20}Cl_2F_2O_4$	**11b**	237–239
4c	CH_3	H	Cl	H	$CH(p\text{-}C_6H_4F)_2$	amorphous	0.10 (1)	83 (3)	$C_{26}H_{23}ClF_2O_4$	**11c**	*h*
4d	CH_3	H	CH_3	H	$CH(p\text{-}C_6H_4F)(p\text{-}C_6H_4OCH_3)$	*h*	0.12 (1)	85 (3)	$C_{28}H_{29}FO_5$	**11d**	232–234
4e	CH_3	H	CH_3	H	$CH(p\text{-}C_6H_4F)(m\text{-}C_6H_4CF_3)$	*h*	0.16 (1)	79 (3)	$C_{28}H_{26}F_4O_4$	**11e**	236–237
4f	CH_3	H	CH_3	H	$CH(p\text{-}C_6H_4F)CH_3$	110–112[i]	0.21 (1)	45 (3)	$C_{22}H_{25}FO_4$	**11f**	*h*
4g	CH_3	H	CH_3	H	$CH(p\text{-}C_6H_4F)i\text{-}Bu$	*h*	0.24 (1)	81 (3)	$C_{25}H_{31}FO_4$	**11g**	*h*
4h	Cl	H	CH_3	H	$CH(m\text{-}CH_3\text{-}p\text{-}F\text{-}C_6H_3)_2$	77–78	0.26 (1)	81 (3)	$C_{28}H_{27}ClF_2O_4$	**11h**	*h*
4i	Cl	H	Cl	H	$CH(m\text{-}CH_3\text{-}p\text{-}F\text{-}C_6H_3)_2$	62–63	0.26 (1)	88 (3)	$C_{27}H_{24}Cl_2F_2O_4$	**11i**	*h*
4j	Cl	H	Cl	H	$CH(p\text{-}C_6H_4F)[(CH_2)_2O(p\text{-}C_6H_4F)]$	glass	0.19 (1)	86 (3)	$C_{27}H_{24}Cl_2F_2O_5$	**11j**	*h*
4k	CH_3	H	Cl	H	$(CH_2)_3O(p\text{-}C_6H_4F)$	98–99	0.19 (1)	67 (3)	$C_{22}H_{24}ClFO_5$	**11k**	*h*
4l	CH_3	H	H	H	$(CH_2)_3O(p\text{-}C_6H_4F)$	*h*	0.19 (1)	72 (3)	$C_{22}H_{25}FO_5$	**11l**	*h*
4m	CH_3	H	Cl	H	$(CH_2)_3O(p\text{-}C_6H_4Cl)$	70–71	0.19 (1)	55 (3)	$C_{22}H_{24}Cl_2O_5$	**11m**	*h*
4n	c-C_5H_9	H	Cl	H	$(CH_2)_3O(p\text{-}C_6H_4F)$	glass	0.20 (1)	79 (3)	$C_{26}H_{30}ClFO_5$	**11n**	*h*
4o	c-C_5H_9	H	H	H	$(CH_2)_3O(p\text{-}C_6H_4F)$	glass	0.20 (1)	94 (3)	$C_{26}H_{31}FO_5$	**11o**	*h*
4p	Cl	H	Cl	H	CO-c-C_6H_{11}	*h*	0.16 (1)	88 (3)	$C_{19}H_{22}Cl_2O_5$	**11p**	*h*
4r	CH_3	H	CH_3	H	$(S)\text{-}CH(c\text{-}C_6H_{11})O_2CC(CH_3)_2CH_2CH_3$	glass	0.19 (1)	90 (3)	$C_{27}H_{40}O_6$	**11r**	*h*
4s	CH_3	H	CH_3	H	$(R)\text{-}CH(c\text{-}C_6H_{11})O_2CC(CH_3)_2CH_2CH_3$	glass	0.17 (1)	92 (3)	$C_{27}H_{40}O_6$	**11s**	*h*
4t	CH_3	H	CH_3	H	$CH_2\text{-}c\text{-}C_6H_{11}$	123	0.20 (1)	68 (3)	$C_{21}H_{30}O_4$	**11t**	*h*
4u	Cl	H	Cl	H	$CH_2\text{-}c\text{-}C_6H_{11}$	92–93[g]	0.16 (1)	81 (3)	$C_{19}H_{24}Cl_2O_4$	**11u**	*h*
4v	CH_3	H	Cl	H	$CH_2\text{-}c\text{-}C_6H_{11}$	89–91	0.20 (1)	78 (3)	$C_{20}H_{27}O_4Cl$	**11v**	*h*
4w	CH_3	H	CH_3	H	$(S)\text{-}CH(c\text{-}C_6H_{11})NHCOC(CH_3)_2CH_2CH_3$	amorphous	0.08 (1)	83 (3)	$C_{27}H_{41}NO_5$	**11w**	*h*
4x	CH_3	H	CH_3	H	$(R)\text{-}CH(c\text{-}C_6H_{11})NHCOC(CH_3)_2CH_2CH_3$	199	0.07 (1)	73 (3)	$C_{27}H_{41}NO_5$	**11x**	*h*
4y	Cl	H	Cl	H	$CF{=}c\text{-}C_6H_{10}$	glass	0.18 (1)	84 (3)	$C_{19}H_{21}Cl_2FO_4$	**11y**	*h*
4z	CH_3	H	CH_3	H	$CH\text{-}c\text{-}C_6H_{11}(p\text{-}C_6H_4F)$	foam	0.20 (1)	90 (3)	$C_{27}H_{33}FO_4$	**11z**	*h*
4aa	*i*-Pr	H	Ph	H	$CH_2\text{-}c\text{-}C_6H_{11}$	glass	0.26 (1)	84 (3)	$C_{28}H_{36}O_4$	**11aa**	*h*
4bb	Cl	H	Cl	H	Ph	amorphous	0.11 (1)	75 (3)	$C_{18}H_{16}Cl_2O_4$	**11bb**	*h*
4cc	Cl	H	Cl	OCH_2-(p-C_6H_4F)	H	amorphous	0.31 (2)	87 (3)	$C_{19}H_{17}Cl_2FO_5$	**11cc**	*h*
4dd	*i*-Pr	–CH=CHCH=CH–		H	$CH(p\text{-}C_6H_4F)_2$	171–173	0.23 (1)	88 (3)	$C_{32}H_{30}F_2O_4$	**11dd**	*h*
4ee	CH_3	–CH=CHCH=CH–		H	$CH(p\text{-}C_6H_4F)_2$	177–179	0.16 (1)	67 (3)	$C_{30}H_{26}F_2O_4$	**11ee**	*h*
4ff	*i*-Pr	H	*i*-Pr	H	$p\text{-}C_6H_4F$	145–146	0.25 (1)	83 (3)	$C_{24}H_{29}FO_4$	**11ff**	243–245
10ff[j]	*i*-Pr	H	*i*-Pr	H	$p\text{-}C_6H_4F$	63–65	0.15 (4)	74 (2)	$C_{28}H_{39}FO_5$	**11ff**[j,k]	230–233
4ff[j,l]	*i*-Pr	H	*i*-Pr	H	$p\text{-}C_6H_4F$	142–144	0.26 (1)	68 (2)	$C_{24}H_{29}FO_4$		
4ff	*i*-Pr	H	*i*-Pr	H	$p\text{-}C_6H_4F$	143–145	0.24 (1)	81 (1)	$C_{24}H_{29}FO_4$		
4gg	*i*-Pr	H	*t*-Bu	H	$p\text{-}C_6H_4F$	178–180	0.28 (1)	75 (3)	$C_{25}H_{31}FO_4$	**11gg**	256–259
4hh	*i*-Pr	H	$p\text{-}C_6H_4F$	H	$p\text{-}C_6H_4F$	190–192	0.23 (1)	82 (3)	$C_{27}H_{26}F_2O_4$	**11hh**	235–237
4hh	*i*-Pr	H	$p\text{-}C_6H_4F$	H	$p\text{-}C_6H_4F$	189–191	0.22 (1)	82 (1)	$C_{27}H_{26}F_2O_4$	**11hh**	235–237

mono-16ii	*i*-Pr	H	$SC(CH_3)_2SR^m$	H	*p*-C_6H_4F	glass	0.20 (5)	75 (1)	$C_{43}H_{52}F_2O_6S_2$	mono-11ii	185–210
di-10ii	*i*-Pr	H	$SC(CH_3)_2SR^m$	H	*p*-C_6H_4F	glass	0.35 (6)	73 (1)	$C_{53}H_{70}F_2O_{10}S_2$	di-11ii	(225) 250–300[n]
10jj	*i*-Pr	H	S(*p*-C_6H_4F)	H	*p*-C_6H_4F	glass	0.18 (3)	81 (1)	$C_{31}H_{36}F_2O_6S$	11jj	192–195
4jj	*i*-Pr	H	S(*p*-C_6H_4F)	H	*p*-C_6H_4F	108–110	0.26 (1)	85 (1)	$C_{27}H_{28}F_2O_6S$	11jj	193–196
10kk	*i*-Pr	*i*-Pr	OAc	*p*-C_6H_4F	*i*-Pr	61–63	0.20 (4)	76 (1)	$C_{33}H_{47}FO_7$	11kk[o]	239–240
10ll	*i*-Pr	*i*-Pr	OAc	*i*-Pr	*p*-C_6H_4F	120–122	0.20 (4)	71 (1)	$C_{33}H_{47}FO_7$	11ll[o]	239–242
4mm[p]	CH_3	–CH=CHCH=CH–		*p*	*p*-C_6H_4F	132–134	0.09 (1)	82 (3)	$C_{22}H_{20}FNO_4$	11mm[p]	*h*
4nn[p]	*i*-Pr	–CH=CHCH=CH–		*p*	*p*-C_6H_4F	124–128	0.12 (1)	83 (3)	$C_{24}H_{24}FNO_4$[q]	11nn[p]	*h*
4oo[p]	Ph	–CH=CHCH=CH–		*p*	CH_3	155–157	0.24 (2)	83 (3)	$C_{22}H_{21}NO_4$	11oo[p]	*h*
4pp[r]	Cl	H	Cl	H	$CH(p\text{-}C_6H_4F)_2$		0.21 (1)	83 (3)	$C_{28}H_{20}Cl_2F_2O_3S$	11pp[r]	*h*
4qq	Cl	H	Cl	H	CF_2-*c*-C_6H_{11}	*g*,*s*	0.33 (7)	40[u]	$C_{19}H_{22}ClF_2O_4$[v]	11qq	*h*
4rr	CH_3	H	CH_3	H	CHCl-*c*-C_6H_{11}	glass	0.21 (1)	76[w]	$C_{21}H_{29}ClO_4$		

[a] Obtained from chromatographically purified compound; not recrystallized unless otherwise noted. [b] TLC plates silica gel $60F_{254}$ Merck, layer thickness 0.25 mm; (1) cyclohexane (CH)/ethyl acetate (EA) 1:1, (2) 100% EA, (3) CH/EA 2:1, (4) CH/EA 3:1, (5) toluene/EA 7:1, (6) $CHCl_3/CH_3OH$ 9:1, (7) CH_2Cl_2/EA 4:1. [c] Isolated yields after chromatography on silica gel, based on direct precursor **10**, **16**, or **25**. [d] Procedures 1, 2, and 3 refer to Schemes I, II, and III, respectively. [e] Analytical results were within ±0.4% of the theoretical value unless noted. [f] Yield from **4** or **10** >95% unless otherwise noted. Substituents R^2–R^6 are the same as for **4**. [g] Recrystallized from *i*-Pr_2O/*n*-hexane. [h] Not determined. [i] Recrystallized from EA/CH. [j] 62% ee. [k] Yield 80%. [l] Prepared from **11ff** via mixed anhydride. [m] See Scheme X. [n] Turns dark at 225 °C, melts with decomposition at 250–300 °C. [o] Acetate saponified; see Scheme X. Compounds contain 1 equiv of NaOAc. [p] β-Quinolinoxy subunit; atom carrying R^5 in formulae **4** and **11** is N. [q] N: calcd, 3.42; found, 2.93. [r] Thiophenoxy subunit; atom A in formula **2** is S. [s] Sinters at >55 °C. [t] 75% yield after freeze-drying of aqueous solution. [u] Based on **4y**, after chromatographic purification. See Scheme X. [v] No elemental analysis. Fully characterized by ^1H, ^{13}C, ^{19}F NMR, and MS (see supplementary material). [w] Based on **25q**, after chromatographic purification. See Scheme X.

Scheme VII.[a] Synthesis of Phenols and β-Naphthols **8aa–ee**



[a] (a) *i*-PrMgCl/−70 °C; (b) DDQ/−40 °C → 25 °C; (c) c-Hex-CH_2MgBr/−70 °C; (d) Raney Ni/H_2; (e) $NaNO_2$/HBr; (f) H_2O/reflux; (g) Cl_2/AcOH/20 °C/3 h; (h) *p*-$FC_6H_4CH_2Br$/NaOH/DMF/100 °C/4 h; (i) 4 equiv *p*-FC_6H_4MgBr/THF/25 °C; (j) Pd/C/H_2/AcOH/HCl; (k) $CHCl_3$/NaOH/H_2O/75 °C; (l) 1 equiv Na/CH_3OH; (m) 4 equiv *i*-PrBr/toluene/reflux; (n) $[(CH_3OCH_2CH_2O)_2AlH_2]Na$ (Red-Al)/xylene/135 °C.

to well-established chemistry; however some features deserve comment.

When ketone **8p** (Scheme VI) was treated with (diethylamido)sulfur trifluoride (DAST), replacement of the carbonyl oxygen by two geminal fluorine atoms was expected.[34] However, vinyl fluoride **8y** was obtained instead, independent of the excess of DAST used. Attempts to achieve the addition of hydrogen fluoride to the double bond of **8y** were unsuccessful using dry HF or synthetic equivalents. However, when **8y** was transformed to β-hydroxy lactone **4y** according to Scheme III, and then was treated with dry HF, the addition occurred without difficulty to give the desired geminal difluoride **4qq** (Scheme X). We attribute the atypical behavior of **8p**'s carbonyl to the proximity of the free phenolix hydroxyl group.

In studies with **1** it has been demonstrated that the sterically demanding ester group contributes significantly to biological activity.[35] While the alcohol resulting from hydrolysis of α-methylbutanoic acid ester **1** has retained only 0.1–0.2%[35] of mevinolin's activity, replacement of the

(33) For uniformity of Tables and Schemes phenols, β-naphthols, β-quinolinols, and thiophenols were all assigned compound no. **8**.

(34) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

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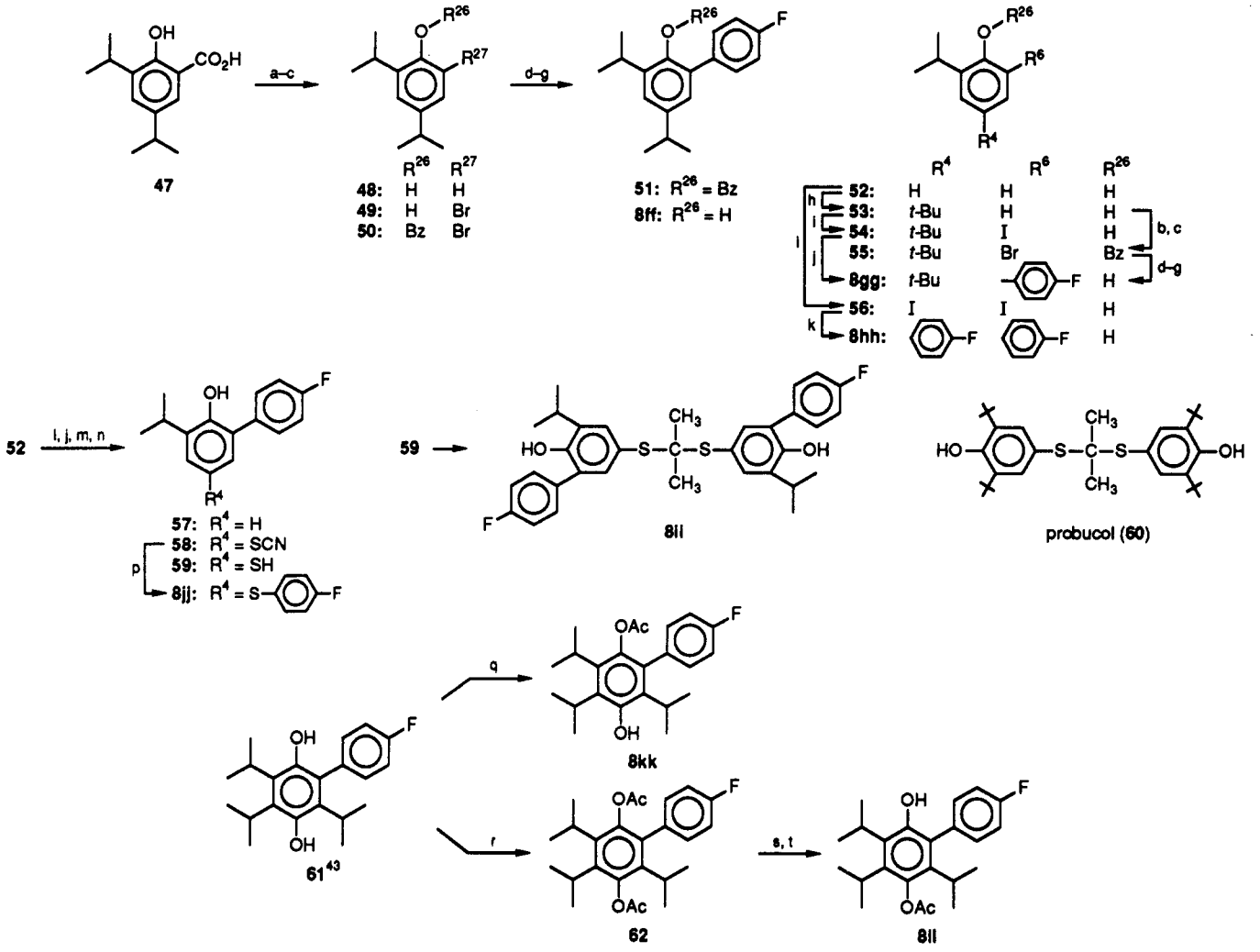
Scheme VIII.[a] Pd(0)-Catalyzed Arylation of Phenols. Synthesis of Phenols 8ff–ll



[a] (a) Quinoline/cat. $2CuO{\cdot}Cr_2O_3$/190 °C; (b) Br_2/CCl_4/10 °C; (c) $BzCl/K_2CO_3$/2-butanone/reflux; (d) Mg/cat. I_2/THF/reflux; (e) *p*-FC_6H_4I/2 mol % $(PPh_3)_4Pd$/THF 20 °C → 55 °C; (f) Raney Ni/EtOH/25 °C/filtration; (g) Pd/C/H_2 (1 bar)/EtOH/25 °C; (h) $CH_3OC(CH_3)_3/ZrCl_4/CH_2Cl_2$/0 °C; (i) I_2/KI/H_2O/$EtNH_2$/25 °C; (j) 3 equiv FC_6H_4MgBr/1 mol % $(PPh_3)_4Pd$/THF/25 °C → reflux; (k) 4 equiv FC_6H_4MgBr/1 mol % $(PPh_3)_4Pd$/THF/reflux; (l) $BrN(CH_3)_2/CCl_4$/−10 °C → 0 °C; (m) $NaSCN/Br_2/CH_3OH$/10 °C; (n) $LiAlH_4$/THF/reflux; (o) $(CH_3O)_2C(CH_3)_2$/cat. TsOH·H_2O/benzene/reflux; (p) *p*-FC_6H_4MgBr/THF/40 °C; (q) 1.3 equiv Ac_2O/2.0 equiv NEt_3/1 mol % DMAP/CH_2Cl_2/−18 °C/2 days; (r) 4 equiv Ac_2O/pyridine/25 °C; (s) 1.1 equiv LiOH/H_2O/$CH_3O(CH_2)_2OCH_3$/25 °C/3 days; (t) chromatographic separation from **8kk**.

α-methylbutanoic acid ester by an α,α-dimethylbutanoic acid ester (to give synvinolin) potentiates the activity by a factor of 2.5.[3] Molecular models of synvinolin and the respective *S* configurated ester **4r** may be superimposed (Figure 1). A good matching of the structures can be achieved, if the molecular models are fitted so as to minimize the distances of corresponding atoms in the lactone and ester moieties.

In the superposition (Figure 1) the aromatic ring of **4r** mimics the cyclohexenyl moiety of synvinolin. The *o*-methyl substituent of **4r** is spatially situated between the methyl group and the bridge methylene (A = CH_2) of synvinolin. To avoid elaborate protecting/deprotecting strategies of the phenol component during the preparation of ester **4r**, we did not synthesize the respective phenol **8r**, but converted **8q** to the β-silyloxy lactone **25q** instead. Treatment of **25q** with α,α-dimethylbutanoyl chloride[3] did not produce the expected mixture of diastereomeric esters **25r**/**25s**, but gave the diastereomeric chlorides **25rr** (Scheme X), which were converted to **4rr**. However, refluxing of a toluene solution of the HPLC-separated diastereomeric alcohols **25q** and α,α-dimethylbutanoic anhydride[36] in the presence of DMAP furnished esters **25r** and **25s** (Scheme VI), which were converted to hydroxy lactones **4r** and **4s**.

In an attempt to transform benzylic alcohol **25q** (Scheme VI) to the corresponding fluoride, it was stirred with 48% aqueous hydrogen fluoride in acetonitrile. Unexpectedly, the corresponding diastereomeric acetamides were obtained. Obviously, the benzylic cation generated from **25q** had been trapped by acetonitrile, resulting in the formation of a carbiminium ion, which then had been trapped by water. The reaction was repeated, utilizing 2,2-dimethylbutyronitrile, to give diastereomeric amides **25w** and **25x**, which could be separated chromatographically. Surprisingly, the silyl protection of the β-hydroxy lactone moiety of **25w,x** was fully retained under the reaction conditions. Additionally, the reaction does not seem to respond to sterical hindrance. Considering the forcing conditions necessary to esterify **25q** to **25r,s** or desacylmevinolin to synvinolin,[36] the smooth formation of **25w,x** at 25 °C is remarkable. Assignments of absolute config-

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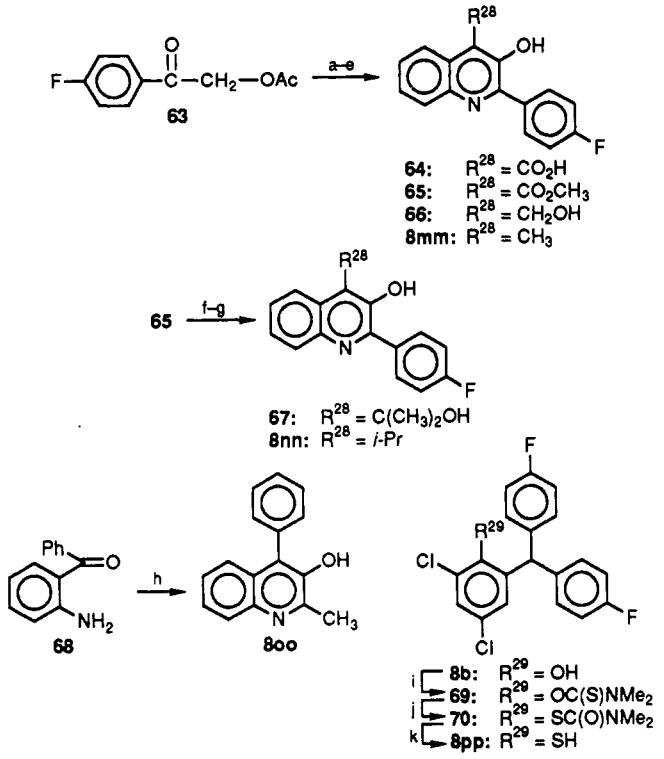
Scheme IX.[a] Synthesis of β-Quinolinols **8mm–oo** and of Thiophenol **8pp**[33]



[a] (a) Isatine/EtOH/6 N aqueous KOH/reflux; (b) concentrated aqueous HCl/0 °C; (c) CH_2N_2/Et_2O/0 °C; (d) $LiAlH_4/Et_2O$; (e) Pd/C/H_2/AcOH, concentrated aqueous HCl; (f) 5 equiv CH_3MgI/THF/25 °C; (g) 67% aqueous HJ/ref P/130–150 °C; (h) CH_3COCH_2OH/AcOH/H_2O/cat. H_2SO_4/reflux/4 h; (i) $(CH_3)_2NCSCl$/DMF/80 °C; (j) 275 °C/30 min; (k) $LiAlH_4/Et_2O$.

uration to the benzylic carbons (*) of esters **25r,s** and amides **25w,x** are tentative.[37]

Aliphatic alkyl groups can be introduced into the ortho or para position of substituted nitrobenzenes by the method of Bartoli and Kienzle.[38] Accordingly, we obtained **39** from *p*-nitrobiphenyl (**37**; Scheme VII). However, an attempt to introduce a *p*-fluorophenyl substituent into **38** in an analogous fashion failed. Nitro compound **39** was converted to the corresponding phenol **8aa** via reduction and deamination.[39] An isopropyl substituent could be introduced into the activated ortho position of β-naphthol **45** by a nucleophilic substitution reaction with isopropyl bromide to give **8dd**. Analogous reactions with methyl iodide or methyl *p*-toluenesulfonate did not give significant amounts of the ortho-methylated naphthol **8ee**. Therefore **8ee** had to be prepared via Reimer-Tiemann formylation[40] and reduction of the aldehyde **46** with Red-Al.[41]

In studies with HMG-CoA reductase inhibitors **2** containing heterocyclic aromatic moieties R, we obtained very potent compounds, when a *p*-fluorophenyl substituent and an isopropyl substituent were present in the aromatic heterocycle R in the two ortho positions to the bridge A–B.[1,2] Consequently, we were highly interested to prepare requisite phenoxy analogues **4**. However, phenols of this special substitution pattern were unknown, because no general method had been reported for the direct arylation of phenols.[42,43] Despite the high tolerance of oxygen functionality in palladium-catalyzed bond formation,[44] the methodology of palladium(0)-catalyzed couplings[45,46] had not been extended to the arylation of phenols. Scheme VIII summarizes the syntheses of the desired phenols **8ff–ll** based on this principle. Whereas **8ff** was prepared via the coupling of a metallorganic phenol component (Grignard of **50**) with a halobenzene, the reactivity of the components was reversed to obtain the double coupling product **8hh** or the ortho-arylation product **57**: halogenated phenols were coupled with arylmagnesium halides. **8gg** was prepared according to both variants. Zirconium-(IV)-induced para-*tert*-butylation of **52** was achieved, following the method of Sartori et al.[47] The palladium-(0)-catalyzed arylation of phenols provided the means to prepare molecules that are hybrids of the structural elements of the established antiatherosclerotic agent probucol (**60**) and of HMG-CoA reductase inhibitors. Probucol has been recently demonstrated to potently inhibit the oxidation of LDL particles in vivo, thus interfering with a strongly atherogenic process[48–50] in addition to its moderate hypocholesterolemic action.[51–53] From the chemical viewpoint, the reasons for probucol's selective and efficacious antioxidative (free radical trapping) activity are (a) *p*-hydroxymercaptobenzene moieties (hydroquinone analogue), the hydroxy groups each being shielded by two bulky *o*-*tert*-butyl substituents; (b) the prevailing transport of plasma–probucol in LDL particles, because of its highly lipophilic properties.[51,52]

The bulky ortho substituents are essential, since they still allow probucol to transfer the phenolic hydrogen atom to a free radical, but they inhibit the resulting phenoxyl radical to propagate the radical chain reaction due to steric inhibition.[54] Since an isopropyl and a *p*-fluorophenyl substituent still exert appreciable shielding to the neighboring hydroxyl, we reasoned that probucol's *tert*-butyl groups may be exchanged with these substituents, without loosing the ability to inhibit LDL oxidation. This was born out by experiment. Both equivalent phenol groups of **8ii** can be coupled with synthon **7a** according to Scheme I. We prepared the monocoupling product mono-**9ii** as well as the dicoupling product di-**9ii** and converted them to the

(37) Assignments are based on the better biological potency and on the larger R_f value (silica, cyclohexane/ethyl acetate) of **25r** and **25w**.

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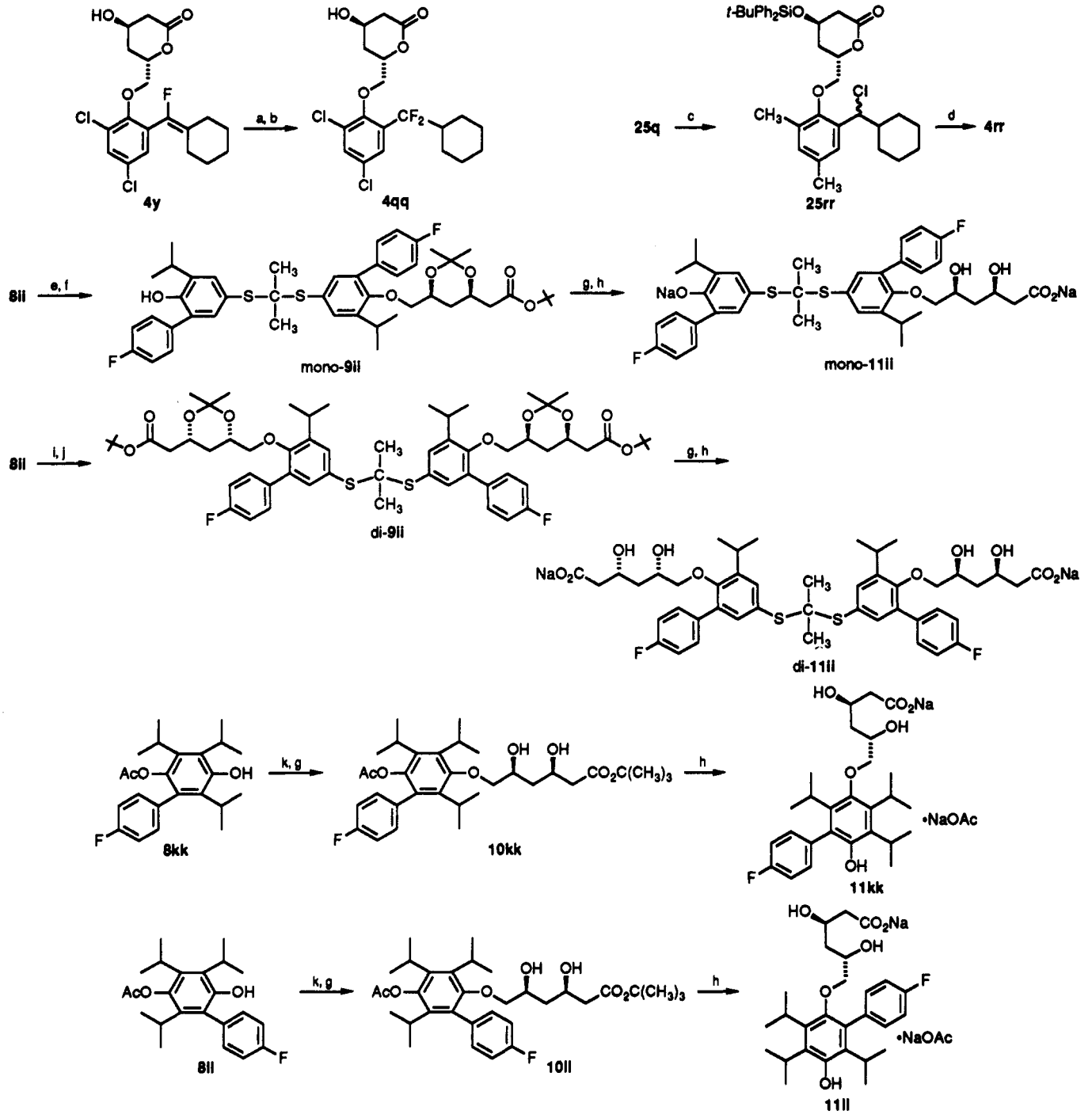
(54) Pryor, W. A.; Strickland, T.; Church, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 2224.

Scheme X[a]



[a] (a) dry HF(l)/0 °C/5 h; (b) SiO_2 chromatography; (c) 3 equiv $CH_3CH_2C(CH_3)_2COCl$/3 equiv DMAP/5 equiv pyridine/CH_2Cl_2/25 °C/1 h; (d) $(n\text{-}Bu)_4NF\cdot 3H_2O$/AcOH/THF/0 °C; (e) 1.2 equiv **7a**/2.4 equiv K_2CO_3/HMPT/cat. 18-crown-6/80 °C/12 h; (f) removal of **di-9ii** by SiO_2 chromatography; (g) 2 N aqueous HCl/THF/EtOH/25 °C/16 h; (h) 2 equiv aqueous 1 N NaOH/EtOH/25 °C/3 h; (i) 4.0 equiv **7a**/8.0 equiv K_2CO_3/HMPT/cat. 18-crown-6/80 °C/12 h; (j) removal of **mono-9ii** by SiO_2 chromatography; (k) 1.65 equiv **7a**/3.3 equiv K_2CO_3/DMSO/cat. 18-crown-6/85 °C/12 h.

respective sodium carboxylates **mono-11ii** and **di-11ii**.

Taking advantage of their slightly different steric shielding, the two hydroxy groups of hydroquinone **61** could be selectively acetylated (Scheme VIII). In the DMAP-catalyzed reaction at −18 °C of **61** with 1.3 equiv of acetic anhydride, **8kk** was obtained in 70% yield, with only a trace of its regioisomer **8ll**. Diacetate **62**, obtained with 4 equiv of acetic anhydride at 25 °C, was monosaponified with moderate selectivity to give **8ll** and **8kk** in a ratio of 2:1, the latter being removed by chromatography. **8kk** and **8ll** were converted to sodium carboxylates **11kk** and **11ll**, respectively, according to Scheme I. The acetoxy protecting group was saponified by sodium hydroxide in parallel to the *tert*-butyl ester, as outlined in Scheme X. β-Quinolinols **8mm** and **8nn** (Scheme IX) were prepared by a condensation reaction of **63** with isatine as the key step, in analogy to the method of Kaslow et al.[55] In **8oo** the aliphatic and the aromatic substituent have changed places. It was obtained by condensation of α-hydroxy-

(55) Kaslow, C. E.; Moe, H. *J. Org. Chem.* **1960**, *25*, 1512.

Table II. Inhibition of Solubilized Rat Liver HMG-CoA Reductase in Vitro[a]

no.	IC_{50},[b] nM	rel[c] pot.	no.	IC_{50},[b] nM	rel[c] pot.
11a	70	10	**11y**	95	9
11b	50	13	**11z**	95	8
11c	70	10	**11aa**	400	2
11d	100	7	**11bb**	190	5
11e	90	7	**11cc**	260	3
11f	160	5	**11dd**	380	2
11g	140	5	**11ee**	900	1
11h	270	2	**11ff**	2.7	300
11i	1000	1	**11gg**	400	2
11j	150	4	**11hh**	17	43
11k	80	10	mono-**11ii**[d]	30	15
11l	250	3	di-**11ii**[d]	10	37
11m	50	15	**11jj**	6	113
11n	>1000	<1	**11kk**	4	171
11o	>1000	<1	**11ll**	20	34
11p	190	4	**11mm**	1000	1
11r	60	12	**11nn**	50	16
11s	500	1	**11oo**	>1000	<1
11t	100	9	**11pp**	950	1
11u	27	31	**11qq**	85	9
11v	75	12	**4rr**[e]	>1000	<1
11w	320	2	mevinolin (1)[f]	8	100
11x	470	1			

[a] The assay system described in ref 1 was used. [b] IC_{50} values were determined by using four or five concentrations of each inhibitor. [c] For estimation of relative inhibitory potencies, mevinolin was assigned a value of 100. The IC_{50} value of test compound was compared with that of mevinolin, corrected for the somewhat different molecular weight. [d] See Scheme X. [e] Lactone form. [f] Sodium carboxylate form.

acetone with o-aminobenzophenone.[56] Phenol **8b** was transformed to the corresponding thiophenol **8pp** (Scheme IX) via a Newman–Kwart rearrangement.[57]

Biological Results

The optically pure sodium salts **11** were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase in vitro (Table II) and to inhibit *cellular* HMG-CoA reductase in cultures of hepatic cells (HEP G2, a human hepatoma cell line), as determined by the inhibition of the incorporation of sodium [^{14}C]acetate into cholesterol (Table III). The latter method has both advantages and disadvantages compared with the inhibition of isolated lyophylized enzyme according to Table II. The cell culture test (Table III) incorporates the phenomena of drug uptake into the living cells and the distribution of the drug into the diverse cell compartments, as well as intracellular drug metabolism and possibly drug's toxicity to the cells. It allows for recognition of inhibition of cholesterol biosynthesis, regardless of the specific enzyme that is inhibited. HMG-CoA reductase inhibition may be observed, as well as inhibition of any other enzyme that is relevant on the biosynthetic pathway that leads to cholesterol. In contrast, inhibition of the isolated enzyme in vitro (Table II) is specific for HMG-CoA reductase and does not include the phenomena of uptake, distribution, elimination, and toxicity of the drug. In conclusion, the cell test treats cholesterol biosynthesis inhibition on a higher level, but the enzyme test is more specific and allows for a classification of the inhibitor type and a distinction of competitive and noncompetitive inhibitors.

Selected compounds were evaluated for their ability to inhibit hepatic de novo cholesterol synthesis in male rats after po administration, as determined by the inhibition

Table III. Inhibition of Acetate Incorporation into Cholesterol in HEP G2 Cells[a]

no.[b]	IC_{50},[c] nM	rel[d] pot.
mevinolin (1)[e]	50	100
11r	12000	<1
11s	1700	3
11w	15000	<1
11x	10000	<1
11aa	100	50
11dd	3500	2
11ee	20000	<1
4ff	1.8	250[f]
11ff	30	150 (170)[g]
11gg	>500	<10
11hh	55	90
mono-**11ii**	>1700	<3
di-**11ii**	>1000	<5
11jj	0.5	10000
11kk	4.1 (7.1)[h]	1200 (700)[h]
11ll	5.6 (28)[h]	900 (180)[h]
11mm	>5000	<1
11nn	250	20
11oo	>5000	<1
11qq	2500	2
4rr	6500	<1

[a] Assay described in ref 1. [b] For structure see Table I. [c] IC_{50} values varied somewhat for different batches of cells. Mevinolin sodium salt averaged IC_{50} = 50 nM and was used in every run as an internal standard. The measured IC's for test compounds **11** were corrected for deviations of mevinolin's IC from its average value. [d] Mevinolin was assigned a value of 100. Potencies were obtained by comparison of test compounds **11** with the internal standard mevinolin. [e] Sodium dihydroxy carboxylate form, optically pure. [f] Lactone form of mevinolin IC_{50} = 4.6 nM. [g] Determined with a rat hepatocyte cell culture. [h] Lowest activity determined in a set of experiments with different batches of HEP G2 cells.

Table IV. Inhibition of Hepatic Cholesterol De Novo Synthesis in Vivo (Rat, Orally, 5 mg/kg of body wt)[a]

no.	% cholesterol de novo synthesis	rel pot.
no drug	100.0	
4a	71.6	33
4b	65.6	40
4m	25.2	87
4u	36.4	74
4ff	11.4	103
4gg	95.7	6
4hh	84.5	18
mevinolin (1)[b]	14.0	100

[a] Assay described in ref 58d. [b] Lactone form, optically pure.

of the incorporation of sodium [^{14}C]octanoate[58] into hepatic cholesterol (Table IV).

Selected compounds were further evaluated for their ability to decrease plasma cholesterol levels in normolipemic NZW rabbits (Table V) and male beagle dogs (Table VI) after po administration. All these tests were also conducted under the same experimental conditions with mevinolin. The respective results are included in Tables II–VI.

Sodium carboxylates mono-**11ii** and di-**11ii**, intended to be hybrids of antioxidants and HMG-CoA reductase inhibitors (vide supra and infra), were additionally eval-

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(57) Newman, M. S.; Hetzel, F. W. *Org. Synth.* **1971**, *51*, 139. Kwart, H.; Omura, H. *J. Am. Chem. Soc.* **1971**, *93*, 7250.
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(59) Granzer, E.; Mauz, O.; Weiser, G.; Müller, K. R. 7th International Symposium on Drugs Affecting Lipid Metabolism, Milan, May 28–31, 1980; Abstract Book, p 187.
(60) Windholz, M., Ed. *The Merck Index*, 10th ed.; Merck & Co., Inc.: Rahway, NJ, 1983; no. 2340, p 338.

Table V. Hypocholesterolemic Activity in Vivo (NZW Rabbits, $n = 5$ or 6, Po)[a]

no.	dosage, mg/kg body wt per day	serum total cholesterol[b]
4a[c]	50	-19
11b[d]	75	-25[e]
4m[c]	50	-2
4u[c]	50	-11
4ff[c]	10	-30
11ff[d]	10	-32
	20[f]	-37
4gg[c]	10	-15
4hh[c]	10	-28
	20[f]	-34
11jj[d]	5	-46
11kk[d]	5	-12
mevinolin (1)[c]	10	-25
	20[f]	-27

[a] Experimental protocol described in ref 1. With a mean value of serum total cholesterol of 40 mg/dL the error limits (SEM) in the experiments varied between 1.3 and 3.2 mg/dL. [b] Percent change relative to control group after oral treatment for 10 days. Continued treatment did not lead to a further decrease of serum total cholesterol levels with any of the compounds listed. [c] Lactone form. [d] Sodium carboxylate form. [e] Four of five rabbits died on continued treatment between 10th and 14th application. [f] 20 mg/kg of body wt per day were administered over a period of 10 days immediately following up the treatment period with 10 mg/kg of body wt per day (that is on 11th - 20th day of the total treatment period). The value given in the table was determined on the 20th day of the total treatment period.

Table VI. Hypocholesterolemic Activity in Vivo (Male Beagle Dogs, $n = 4$, Po)[a]

no.	dosage, mg/kg body wt per day	duration of treatment, days	serum LDL-cholesterol[b]
11ff[c]	10	14	-10
	25	14	-21
4hh[d]	30	21	+3
11hh[c]	25	14	+3
4jj[d]	5	14	-9
	30	14	-21
mevinolin (1)[d]	10	19	-20

[a] For experimental protocol see Experimental Section. With a mean value of serum LDL-cholesterol of 310 μg/mL the error limits (SEM) in the experiments were 44 ± 5 μg/mL. [b] Percent change relative to control group. [c] Sodium carboxylate form. [d] Lactone form.

uated for their effects on serum lipoproteins and other metabolic parameters after subchronic (7 days) po administration to male rats. The data, together with those of clofibrate and probucol, are compiled in Table VII.

Those phenols 8 that possess the structural elements prerequisite for antioxidative/free-radical inhibiting activity and HMG-CoA reductase inhibitors (lactone 4 and sodium carboxylates 11) prepared from building blocks 8 were evaluated for their ability to inhibit microsomal lipid peroxidation and cupric sulfate induced LDL oxidation in vitro (Table VIII).

Examples given in Table IX demonstrate that structure–activity relationships (SAR) for phenoxy-type inhibitors (2, A–B = OCH_2) in some aspects diverge from those of similar systems (2, A–B = CH_2CH_2 or CH=CH).

Discussion

Compounds **11a–e**, carrying a diphenylmethyl substituent in the ortho position of the phenolic core, inhibited solubilized rat liver HMG-CoA reductase with 7–13% of mevinolin's potency. Different substitution of the remaining ortho and para position of the phenolic core (CH_3 or Cl) and of the core of the phenyl substituents (F, CH_3, OCH_3) had only small effects on the solubilized liver enzyme. Lactones **4a** and **4b** inhibited hepatic cholesterol de novo synthesis in rats with 33 and 40%, respectively, of mevinolin's potency, after po administration. The tendency of highly lipophilic chloro(fluoro)-substituted compounds to considerably surpass in vivo (Table IV) the activity expected from their inhibition of solubilized enzyme (Table II) is reflected in compounds with other substitution patterns, too (notably **4m** and **4u**). They inhibited cholesterol synthesis in vivo with 87 and 74%, respectively, of mevinolin's activity, though possessing only 15 and 31%, respectively, of mevinolin's potency to inhibit solubilized HMG-CoA reductase.

Replacements in the bulky ortho substituent of the *p*-fluorophenyl by alkyl groups decreased enzyme inhibition (Table II, compare **11f** and **11g** with **11a**). Surprisingly, the activity dropped considerably when the *p*-fluorophenyl group was replaced by a *p*-fluoro-*m*-methylphenyl group (compare **11h** and **11i** with **11c** and **11b**), indicating strict steric requirements in the enzyme remote from the space probed by reported inhibitors.[8-19]

The bulky ortho substituent R^6 of **11a–i** was replaced by the sterically undemanding but extended 3-phenoxypropyl substituent. The resulting compounds **11k** and **11m** inhibited the solubilized enzyme with 10 and 15%, respectively, and the cholesterol synthesis in vivo with 87% (**4m**) of mevinolin's potency.

Unexpectedly, the *p*-fluorophenyl group was no longer tolerated in the benzylic (α-) position of the 3-phenoxypropyl substituent (Tables II and III, compare **11j** with **11b,c,k,m**). This result implies that the 3-phenoxypropyl substituent has *less* conformational freedom in the enzyme–inhibitor complex than the bulkier and rigid *p*-fluorophenyl group of **11b** or **11c**. The presence of a para substituent R^4 was essential for adequate inhibitory potency (see **11l**). The second ortho substituent R^2 may not be larger than isopropyl (compare **11n,o** with **11k**).

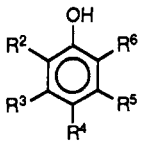
Compound **11p** with a cyclohexylcarbonyl substituent R^6 had low activity. α,α-Dimethylbutanoic acid esters **11r**

Table VII. Effect on Serum Lipoproteins and Other Metabolic Parameters after Subchronic (7 Days) Oral Administration to Male Rats ($n = 10$)[a]

test compound	dosage, mg/kg of body wt per day	% change relative to control group: total cholesterol VLDL	total cholesterol LDL	total cholesterol HDL	liver weight	body weight	cholesterol HDL/LDL[b]
mono-**11ii**	30	+12	-26	+13	+3	+5	1.27
	100	+13	-16	-3	+1	+5	1.15
di-**11ii**	100	-23	-52	+9	-1	+5	2.25
probucol (**60**)[c]	30	+4	-24	-11	+5	+5	0.97
clofibrate (71)[d]	100	-40	-19	-29	+15	+8	0.88
no drug[e]	-					+4	1.00[b]

[a] For protocol see Experimental Section. With a mean value of serum total cholesterol of 87 mg/dL the error limits in the experiments were 4.6 ± 0.8 mg/dL. [b] Value of control group was normalized to 1.00. [c] Formula: Scheme VIII. [d] Formula: p-$ClC_6H_4OC(CH_3)_2CO_2C_2H_5$ (71). [e] Control group.

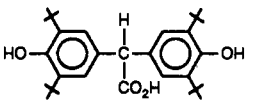
Table VIII. Inhibition of Microsomal Lipid Peroxidation and of Cu^{2+}-Catalyzed LDL Oxidation (in Vitro)[a]



8[b]

no.	inhibn of microsomal lipid peroxidn			inhibn of Cu^{2+}-cat. LDL oxidn		
	IC_{50}, μM	% at 10^{-5} M	rel[c] pot.	IC_{50}, μM	% at 10^{-5} M	rel[c] pot.
mono-11ii	2.7		4			
di-11ii		<10	≪0.1			
4jj				>10	23	<0.1
8jj	3.0	95	3	1.0		11
11jj		<10	≪0.1	>10	41	0.1
8kk	2.8	98	4	0.15		73
11kk		<10	≪0.1	6.0		2
8ll	4.8	83	2			
11ll		27	<0.1	1.1		10
terbuficine[59] (72)[d]	0.1		100[c]	0.11		100[c]
probucol (60)[e]				0.5		22

[a] Assays described in Experimental Section. [b] For definition of R^2–R^6 and structures of 4 and 11, see Table I. [c] Terbuficine (72) was assigned a value of 100. [d] Formula:



[e] Formula: Scheme VIII.

and **11s** of the corresponding alcohol were prepared with the intention to simulate the ester group of synvinolin (vide supra); however this met with only moderate success (**11r**). The corresponding amides **11w** and **11x** had low activity. We concluded that polar functionality (keto, ester, amide) is not tolerated in the α-position of the cyclohexylmethyl substituent R^6, and indeed obtained reasonably active compounds **11t–y** (Tables II and III) when this functionality was omitted. Within this series, again, *o,p*-dichloro substitution (**11u**) was best and led to 74% of mevinolin's in vivo activity (Table IV).

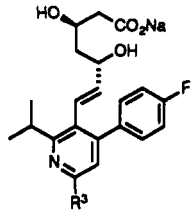
Introduction of one or two fluorine atoms or of *p*-fluorophenyl into the α-position of the cyclohexylmethyl substituent R^6 worsened activity slightly, leading to compounds (**11y,qq,z**) comparable to *o*-diphenylmethyl substitution (e.g. **11b**). Replacement of the phenolic oxygen by sulfur diminished the activity (**11pp**).

There are no "optimal" substituents R^2–R^6 per se. All the substituents are highly interdependent as regards to their optimal shape. For example, the ortho (R^2) substituent isopropyl has been found highly effective in combination with the ortho (R^6) substituent *p*-fluorophenyl and the para (R^4) substituent (substituted) phenyl or isopropyl in several five- and six-membered heterocyclic systems.[1,2,8-14,16,19] This SAR was roughly but not perfectly reflected in the phenoxy systems **11ff–ll** (vide infra). However, the R^6 substituents cyclohexylmethyl or bis(*p*-fluorophenyl)methyl, which had been found effective together with R^2 substituents such as methyl or chloro (vide supra), could not be successfully combined with R^2 = isopropyl (**11aa,dd**). A meta/para-condensed aromatic ring, well-tolerated in the case of *o*-isopropyl, *o'*-(*p*-fluorophenyl) substitution (see 77,[61] Table IX), was not tolerated in the case of *o*-methyl, *o'*-[bis(*p*-fluorophenyl)methyl] substitution (compare **11a** with **11ee**). Up to this point, the reported SAR results are qualitatively consistent with the purely steric model proposed by Roth et al.[14] for systems with a two-carbon bridge (**2**: A–B = CH_2CH_2 or (*E*)-CH=CH). However, we obtained unequivocal evidence that SAR for phenoxy systems **11** partially diverge from this model and that electronic effects cannot always be neglected. The most striking examples are collected in Table IX. In the case of pyridine-based inhibitor **73**[1] substitution of the *p*-isopropyl by the *tert*-butyl group gave **74**,[1] three times more active in enzyme inhibition[1] and more potent in vivo (rabbit po). The same substitution performed on the sterically equivalent, highly efficacious phenoxy system **11ff** gave **11gg**, virtually inactive in vitro and in vivo. Sterically equivalent pyrrole,[2] indole,[61] and pyridine systems[1] (Table IX) had highly consistent inhibitory activity. Substitution of *o*-methyl for *o*-isopropyl uniformly increased activity by a factor of 12–13 and gave compounds with about 3 times mevinolin's potency in vitro. The activity of sterically equivalent quinolinoxy system **11mm** comparably increased, when *o*-methyl was replaced by isopropyl (**11nn**), but both compounds are less active than expected based on purely steric considerations. A comparison of dichlorophenoxy compound **11bb** with sterically equivalent **80**[6c] (Table IX) similarly leads to the conclusion that the electronic effects on efficacy of HMG-CoA reductase inhibition cannot be neglected.

Interesting activities and pharmacological profiles were obtained for the group of compounds **11ff–ll**. **11ff** inhibited HMG-CoA reductase with 3 times the potency of mevinolin (**1**). In the cell test lactone **4ff** and sodium salt **11ff** were 2.5 and 1.5 times, respectively, more active than the corresponding forms of mevinolin. **4ff** inhibited hepatic cholesterol "de novo" synthesis in vivo (rat, po, Table IV) equipotent with mevinolin. **4ff** and **11ff** decreased plasma cholesterol levels (rabbit, po, Table V) equipotently with mevinolin at 10 mg/kg per day and with 150% of mevinolin's efficacy at 20 mg/kg per day. Thus, **11ff** was the first phenoxy-type inhibitor to be successful in a *chronic* in vivo experiment since **4a**, **4m**, and **4u** were not significantly active even in the high dose of 50 mg/kg per

(61) Kathawala, F. G.; Scallen, T.; Engstrom, R. G.; Weinstein, D. B.; Schuster, H.; Stabler, R.; Kratunis, J.; Wareing, J. R.; Jewell, W. F.; Widler, L.; Wattanasin, S. 8th International Symposium on Atherosclerosis, Rome, Oct 9–13, 1988; p 445.

Table IX. Examples for Divergence of SAR, Induced by the Ether Bridge



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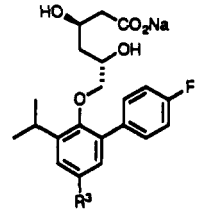
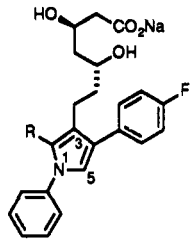
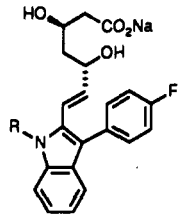


11ff,gg

R^3	no.	IC_{50},[a] nM	in vivo (rabbit, po)[b]	no.	IC_{50},[a] nM	in vivo (rabbit, po)[b]
i-Pr	73[c]	3[c]	very potent	11ff	2.7	very potent
t-Bu	74[c]	1[c]	more potent than 73	11gg	400	not significantly active



75, 76



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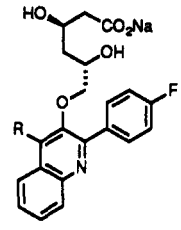
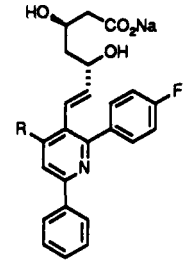
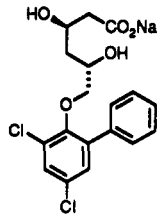


11mm,nn

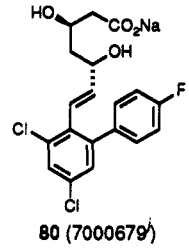


78, 79

R	no.	IC_{50},[a] nM	no.	IC_{50},[a] nM	no.	IC_{50},[a] nM	no.	IC_{50},[a] nM
CH_3	75[d,e]	35[d-f]			11mm	1000	78[c]	38[c]
i-Pr	76[d]	3[d]	77[g]	2.5[f,h] (6.9)[g,i]	11nn	50	79[c]	3[c]



11bb



80 (7000679[j])

no.	IC_{50},[a] nM	no.	IC_{50},[a] nM
11bb	190	80	4.5[h]

[a] Inhibition of solubilized HMG-CoA reductase. Test according to Table II. [b] Test according to Table V. [c] Reported in ref 1. [d] Reported in ref 2. [e] Additional methyl substituent in position 5 of pyrrole. [f] Corrected for inactive enantiomer. [g] Reported in ref 61. [h] Resynthesized in Hoechst AG (1986) and used in test according to Table II for comparison. [i] Difference of reported and measured IC_{50} value probably due to differences in preparation of solubilized, partially purified enzyme. [j] Reported in ref 6c.

day (Table V), despite possessing 33–87% of mevinolin's activity in the *acute* in vivo experiment (Table IV). With 75 mg/kg per day **11b** was significantly active, but toxic, in the rabbit experiment.

Surprising data were obtained with the *o,p*-bis(*p*-fluorophenyl)-substituted system **11hh**. Its enzyme inhibition was reproducibly only 43% of mevinolin's, considerably less than expected by analogy to heterocyclic systems with a two-carbon bridge[1,2] (compare **76**[2] and **79**,[1] Table IX). **11hh** had 90% of mevinolin's potency in the cell test (Table III), only 18% in the acute in vivo (Table IV) test, but 100–150% in the chronic in vivo experiment (Table V). Thus **4hh** decreased plasma cholesterol levels in rabbits as potently as the chemically very similar compound **4ff**, despite exhibiting only 14% of its in vitro and acute in vivo activity.

This enhanced chronic in vivo activity was even more pronounced with **11jj**, which differs from **11hh** only by the introduction of a sulfur atom in para position. **11jj** was only slightly superior to mevinolin in vitro (Table II), but 100 times more active in the cell test, repeatedly (Table III). It reduced plasma cholesterol levels (rabbit po) by 46% at a dosage of only 5 mg/kg per day (Table V), thus being 4–6 times more efficacious than mevinolin. Its phenolic building block **8jj** (a potential metabolite of **11jj**; vide infra) inhibited LDL oxidation in vitro with half of probucol's activity (Table VIII). **11kk** (*o,o'*-diisopropyl substitution) exceeded the enzyme-inhibiting activity of its regioisomer **11ll** by a factor of 5. **11kk** had 7–12 times mevinolin's potency in the cell test, but was not significantly active in the rabbit experiment. Its phenolic building block **8kk** inhibited LDL oxidation 3 times more than probucol, while **11kk** itself had only 9% of probucol's potency. Regioisomeric **11ll** inhibited LDL oxidation with half of probucol's activity.

Compounds mono-**11ii** and di-**11ii** were only moderately active HMG-CoA reductase inhibitors. This is attributed to an excessive bulk of their para substituents R^4 (compare **11gg**). However, both compounds reduced LDL-cholesterol after po administration to male rats (Table VII). Compounds that exclusively act via HMG-CoA reductase inhibition are usually inactive in this modol, due to a fast, intensive enzyme induction that compensates for the inhibition.[62] An improved HDL/LDL ratio, notably for di-**11ii**, was observed.

(62) Endo, A.; Tsujita, Y.; Kuroda, M.; Tanzawa, K. *Biochim. Biophys. Acta* **1979**, *575*, 266.

Unfortunately, all tested phenoxy-type inhibitors had only moderate activity after po administration to male beagle dogs (Table VI). This result was unexpected, since for inhibitors based on heterocyclic systems (carrying the same substituents) in vitro activity correlated well with the in vivo activity in *both* rabbits and dogs.[1,2]

The reason for the decreased oral activity of phenoxy-type inhibitors **11ff**, **4hh** (or **11hh**), and **4jj** in the dog (Table VI), as opposed to their excellent oral activities in the rabbit (Table V), the rat (Table IV), and in vitro (Tables II and III), was not elucidated. However, since investigations of HMG-CoA reductases of several different animal species did *not* indicate relevant species differences of the active site,[63] we presume that a fast metabolic deactivation takes place in the dog. According to the generally accepted mechanism, aryl ethers are metabolically cleaved by an oxidative O-desalkylation.[64] Accordingly, phenoxy-type inhibitors (**2**, A = O) would be oxidized in the α-position (B in **2**). The resulting hemiacetal would be hydrolyzed to give the corresponding phenol **8**, which possesses the desired ability to inhibit LDL oxidation (Table VIII).

In summary, the introduction of an oxygen atom into bridge position A of general formula **2** induced some pronounced and surprising changes of the pharmacological profile. Chemical structure–activity relationships of respective compounds **4** diverged considerably from those of HMG-CoA reductase inhibitors with carbon–carbon bridges (A–B = CH_2CH_2 or CH=CH). The plasma cholesterol lowering activity (rabbit) of some compounds of general formula **4** was considerably stronger than would be expected on the basis of the in vitro potency of these compounds. Although several compounds **4** were highly efficacious in the rabbit, they had only moderate activity in male beagle dogs, whereas heterocyclic inhibitors[1,2] and mevinolin (**1**) exhibited comparable activity in both animal species. Some compounds of general formula **4** exceeded the activity of clofibrate and probucol to reduce plasma LDL-cholesterol levels after subchronic, oral administration to male rats, an activity not generally seen for compounds that exclusively act via HMG-CoA reductase inhibition.[62] Several compounds of general formula **4** inhibited cholesterol biosynthesis *and* oxidation of LDL (at least in vitro), thus interfering with two atherogenic processes simultaneously.

Lactones **4ff** and **4hh**, as well as sodium carboxylates **11ff** and notably **11jj**, exceeded mevinolin's potency in vitro and in vivo (rat, rabbit), but not in the dog.[65] The surprisingly low subchronic toxicity[66] of these compounds renders them attractive as backups of HR 780,[1] which is currently in clinical studies.

Experimental Section

For general remarks see ref 1. All starting materials were commercially available unless indicated otherwise. Compounds **6**,[24] **8ff**,[43] **8hh**,[43] **8ii**,[43] **8jj**,[43] **20**,[32] **48–51**,[43] **53**,[47] **56**,[43] **57–59**,[43] **61**,[43] α,α-dimethylbutanoic anhydride[36] (needed for preparation of **25r** and **25s**), and α,α-dimethylbutyronitrile[67] (needed for preparation of **25w** and **25x**) were prepared as described in the literature. Compounds **54**, **55**, and **8gg** were obtained in analogy to the descriptions given for **8ff**, **8hh**, and **57**.[43]

(3*R*,5*S*)-6-[(Methylsulfonyl)oxy]-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoic Acid *tert*-Butyl Ester (7a). Methanesulfonyl chloride (238 g, 2.08 mol) was added dropwise at 0–5 °C within 1 h to the solution of **6** (360 g, 1.39 mol) in CH_2Cl_2 (1.5 L) and pyridine (1.5 L), and the mixture was stirred for 30 min at 0 °C. The solvents were removed in vacuo. The residue was dissolved in toluene (0.5 L) and washed twice with water, saturated $NaHCO_3$ solution, and with brine. The organic phase was dried ($MgSO_4$), evaporated in vacuo, redissolved in toluene, and re-evaporated. The residual oil was seeded with crystals of **7a**, leading to a quick crystallization. The solid was stirred with cyclohexane (1 L), suction-filtered, and washed with cyclohexane. It was dried in vacuo to give 421 g (1.25 mol, 90% yield) of colorless crystals, mp 76–78 °C. Anal. ($C_{14}H_{26}SO_7$) C, H, S.

(3*R*,5*S*)-6-[(*p*-Tolylsulfonyl)oxy]-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoic Acid *tert*-Butyl Ester (7b). *p*-Toluenesulfonyl chloride (5.8 g, 30.5 mmol) was added in portions at 0–5 °C to the solution of **6** (4.0 g, 15.4 mmol) in CH_2Cl_2 (50 mL) and pyridine (50 mL). The mixture was stirred for 2.5 h at 0 °C and 0.5 h at 20 °C. The solvent was evaporated in vacuo. The residue was redissolved in toluene and washed twice with water, saturated $NaHCO_3$ solution, and brine. The organic phase was dried, concentrated in vacuo, and filtered through 50 g of silica with CH_2Cl_2/EtOAc 30:1. The solvent of the filtrate was evaporated in vacuo to give 5.0 g (12.1 mmol, 78% yield) of colorless crystals (mp 90–93 °C), which were washed with hexane, dried in vacuo, and stored at −25 °C. Anal. ($C_{20}H_{30}SO_7$) C, H, S.

(3*R*,5*S*)-6-Iodo-3,5-*O*-isopropylidene-3,5-dihydroxyhexanoic Acid *tert*-Butyl Ester (7c). NaI (12.5 g, 83.4 mmol) was added to the solution of tosylate **7b** (4.6 g, 11.1 mmol) in acetone (250 mL). The mixture was refluxed (18 h), NaI (7.0 g, 46.7 mmol) was added, and reflux was resumed (6 h), leaving 20% of unreacted **7b** according to TLC. The solvent was evaporated, the residue dissolved in toluene and was washed twice with water and then with brine. The organic phase was dried and concentrated in vacuo, and the residue was chromatographed through 200 g of silica with cyclohexane/EtOAc 4:1, giving 500 mg of unreacted **7b** and 3.4 g (9.2 mmol, 83% yield) of the title compound as a glass. Anal. ($C_{13}H_{23}IO_4$) C, H, I.

In a series of experiments aimed to prepare the corresponding triflate **7d**, no stable product of reasonable lipophilicity could be obtained from **6** and triflic anhydride in pyridine.

Coupling of Phenols 8 with Mesylate 7a To Give Acetonides 9. General Procedure. DMSO or HMPA were employed as the solvent, the latter in case of phenols **8** containing an oxidation-sensitive thio functionality or hydroquinone moieties.

K_2CO_3 powder (1.0 mol) was added to a solution of phenol **8** (0.5 mol) and mesylate **7a** (0.5 mol) in the solvent (1.5 L). 18-Crown-6 (100 mg) was added and the mixture was heated to 60–85 °C, depending on the steric shielding of phenol **8** (reaction time ≈ 12 h). Reaction progress was monitored by TLC (100% toluene or cyclohexane/EtOAc 5:1) until **8** had disappeared. [With sterically hindered **8** it is preferable to add additional **7a** (0.25 mol) after 12 h and to continue the heating for 12 h.] Ice (2 kg), saturated $NaHCO_3$ solution (1 L), and Et_2O (1 L) were added, and the mixture was extracted with Et_2O (3 × 1 L). The combined extracts were washed with $NaHCO_3$ solution and with brine, dried ($MgSO_4$), and concentrated to dryness in vacuo. The residue generally crystallized, when triturated with CH_3OH and scraped: 60–85% yield. Products from very sterically hindered phenols **8** were less pure and needed to be purified by silica chromatography (cyclohexane/EtOAc 10:1 + 0.1% NEt_3): 45–60% yield. **9ff** (solvent DMSO, 75% yield, mp 73–74 °C), **9hh** (DMSO, 85%,

(63) (a) Luskey, K. L.; Stevens, B. *J. Biol. Chem.* **1985**, *260*, 10271. (b) Liscum, L.; Finer-Moore, J.; Stroud, R. M.; Luskey, K. L.; Brown, M. S.; Goldstein, J. L. *J. Biol. Chem.* **1985**, *260*, 522. (c) Chin, D. J.; Gil, G.; Russell, D. W.; Liscum, L.; Luskey, K. L.; Basu, S. K.; Okayama, H.; Berg, P.; Goldstein, J. L.; Brown, M. S. *Nature* **1984**, *308*, 613. (d) Basson, M. E.; Thorsness, M.; Finer-Moore, J.; Stroud, R. M.; Rine, J. *Mol. Cell Biol.* **1988**, *8*, 3797. (e) Woodward, H. D.; Allen, J. M. C.; Lennarz, W. J. *J. Biol. Chem.* **1988**, *263*, 18411.

(64) Mutschler, E. *Arzneimittelwirkungen. Lehrbuch der Pharmakologie und Toxikologie*, 5th ed.; Wissenschaftliche Verlagsgesellschaft: Stuttgart, 1986; p 21.

(65) A referee suggested that the differences seen between dog and other species might not be evident when the more sensitive model of cholestyramine primed dogs is used. Respective studies are ongoing and will be reported elsewhere.

(66) Following a referee's suggestion, data will be reported elsewhere.

(67) Hasek, R. H.; Elam, E. U.; Martin, J. C. *J. Org. Chem.* **1961**, *26*, 1822.

mp 114–115 °C), mono-**9ii** (HMPA, 48% besides 20% of di-**9ii**, mp 49–52 °C), di-**9ii** (HMPA, 8 equiv K_2CO_3, 4 equiv **7a**, 55% besides 15% of mono-**9ii**, mp 47–51 °C), **9jj** (HMPA, 74%, oil), **9kk** (DMSO, 52%, 152–154 °C), and **9ll** (DMSO, 53%, 145–147 °C) were produced.

***tert*-Butyl β,δ-Dihydroxy Carboxylates 10. General Procedure.** A solution of acetonide **9** (0.5 mol) in EtOH (2.5 L), THF (1.25 L), and 2 N hydrochloric acid (280 mL) was stirred for 1 day at ambient temperature. The solution was adjusted to pH 7 with solid $NaHCO_3$. Organic solvents were removed in vacuo, and the residue was divided between Et_2O and water. The aqueous phase was extracted with Et_2O. The combined extracts were washed with water and then with brine, dried ($MgSO_4$), and evaporated in vacuo. **10ff** (95% yield, an oil that slowly crystallized), **10hh** (99%, colorless solid); mono-**10ii**, di-**10ii**, **10jj**, **10kk**, and **10ll** (see Table I) were produced.

Saponification of *tert*-Butyl Esters 10 To Give Sodium Carboxylates 11. General Procedure. 1 N NaOH (10 mL, 10 mmol; in the case of mono-**10ii**, di-**10ii**, **10kk**, and **10ll**, 20 mL, 20 mmol) was added to the solution of ester **10** (10 mmol) in EtOH (75 mL). The reaction mixture was stirred until TLC (CH_2Cl_2/CH_3OH 10:1) indicated disappearance of **10** (usually 2–3 h). The solvent was removed in vacuo. The residue was repeatedly redissolved in CH_3OH or toluene and evaporated to dryness each time. It was washed with *i*-Pr_2O and then with Et_2O and dried in vacuo to give a colorless solid; >95% yield. **11kk** and **11ll** prepared according to this procedure contain 1 equiv of NaOAc.

Cyclization of *tert*-Butyl Esters 10 To Give Lactones 4. General Procedure. Trifluoroacetic acid (55 mL) was added at 0 °C to the solution of ester **10** (100 mmol) in CH_2Cl_2 (200 mL). The mixture was stirred for 2 h at 20 °C. TLC (cyclohexane/EtOAc 1:1) indicated complete transformation. $NaHCO_3$ (50 g) was added portion wise at 0 °C. The mixture was poured into pH 7 buffer and extracted with EtOAc (3 × 100 mL). The extracts were washed with pH 7 buffer, water, and with brine. They were dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was either recrystallized (*i*-Pr_2O/EtOAc 2:1) or purified by chromatography (see Table I).

Coupling of Phenol 8gg with Iodide 7c To Give 9gg and a Stereoisomer. K_2CO_3 powder (540 mg, 3.9 mmol) and hydroquinone (10 mg) were added to a solution of **8gg** (557 mg, 1.95 mmol) and iodide **7c** (725 mg, 1.95 mmol) in DMSO (50 mL). The mixture was stirred under argon at 52–55 °C for 3 h. TLC (toluene/EtOAc 30:1) indicated only small amounts of iodide **7c**, and unreacted phenol **8gg** and a new spot (product) were present in a ratio of about 1:1. Chromatography (200 g silica, toluene) removed **8gg** (300 mg) and gave an oil, which according to HPLC (LiChrosorb Si 60, 10 μm, methylcyclohexane/EtOAc 22:1, 40 °C, 1.0 mL/min, detect 254 nm) consisted of two product peaks (t_R 5.56 and 6.08 min, 39 and 51%) and of **7c** (t_R 7.56 min, 8%). The products were separated by preparative HPLC and characterized by 270-MHz ^1H NMR and MS. Comparison of the NMR with those of compounds **9** (obtained from mesylate **7a**) suggested that the product of smaller t_R was **9gg**, whereas the more polar product was a stereoisomer of **9gg**.

1,1-Diethoxy-2-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]ethane (12ff). K_2CO_3 powder (243 g, 1.76 mol) and then bromoacetaldehyde diethyl acetal (191 g, 0.97 mol) were added to a solution of 2,4-diisopropyl-6-(4-fluorophenyl)phenol (**8ff**; 240 g, 0.88 mol) in DMSO (2 L; dried by passage through basic alumina activity I, immediately before use). The mixture was heated for 10 h to 90 °C. It was cooled and poured into ice/water (5 L). It was extracted with Et_2O (4 × 1 L). The combined extracts were washed with brine and dried, and the solvent was evaporated in vacuo. K_2CO_3 powder (1 g) was added to the residue, and it was distilled in vacuo (without column) to give, after a small prerun, the title compound (298 g, 87% yield) as a colorless oil (bp 148–152 °C/2 × 10^{-4} bar). Anal. ($C_{24}H_{33}FO_3$) C, H, F.

[2,4-Diisopropyl-6-(4-fluorophenyl)phenoxy]acetaldehyde (13ff). 2 N HCl (0.9 L) was added to the solution of acetal **12ff** (287 g, 0.74 mol) in acetone (2.75 L). The mixture was stirred for 5 h at 65 °C and then allowed to cool to 20 °C overnight. The acetone and part of the water was evaporated in vacuo. The residue was taken up in Et_2O. The organic phase was separated and washed with water, saturated $NaHCO_3$ solution, and with brine. The organic phase was dried ($MgSO_4$) and the solvent was evaporated in vacuo. The residue was distilled in vacuo (without column) to give, after a small prerun, the title compound (198 g, 85% yield) as a colorless oil (bp 140–143 °C/1 × 10^{-4} bar), which quickly crystallized. Anal. ($C_{20}H_{23}FO_2$) C, H, F.

(*S*)-2-Hydroxy-1,2,2-triphenylethyl (3*S*)-Hydroxy-4-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]butanoate (14ff). (a). A 1.6 M solution of n-BuLi in hexane (381 mL, 610 mmol) was added at −70 °C under N_2 to a solution of diisopropylamine (90 mL, 636 mmol) in THF (700 mL). The solution was stirred for 30 min at 0 °C. The resulting LDA solution was added via a Flex-needle[68] through septa to a suspension (−70 °C) of (*S*)-(−)-phenyl (2-hydroxy-2,2-diphenylethyl)acetate[28] (93.0 g, 280 mmol) in THF (900 mL). The mixture was allowed to warm up to 0 °C and stirred for 30 min at this temperature. The resulting yellow-orange clear solution was cooled to −90 °C and a precooled solution of [2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]acetaldehyde (**13ff**; 80.0 g, 254 mmol) in THF (250 mL) was added dropwise via a Flex-needle at such a rate that the temperature did not climb above −80 °C. The reaction mixture was stirred for 1 h at −90 °C. The cold mixture was poured into saturated aqueous NH_4Cl solution (2 L) and stirred for 1 h with warming to 25 °C. It was extracted with Et_2O (3 × 1 L), the combined extracts were washed with 20% NaCl solution and dried, and the solvent was evaporated in vacuo. The residue was triturated with *n*-pentane (2 L) and stirred for 30 min. The solid was suction filtered, washed with *n*-pentane and dried in vacuo to give a colorless solid (159 g, 246 mmol, 97% yield). HPLC indicated 60% de. ^1H NMR [Eu(hfc)$_3$] analysis of methyl ester **15ff** prepared from this sample (vide infra) indicated 65% ee. It was generally observed that optical induction as analyzed by NMR was indicated to be 4–5% in excess of the HPLC value. An analytical sample was obtained by recrystallization from warm *i*-Pr_2O, mp 169–171 °C. Anal. ($C_{42}H_{43}FO_5$) C, H, F. HPLC of this sample still indicated 60% de; ^1H NMR [Eu(hfc)$_3$] analysis of **15ff** showed 65% ee. Modification of reaction conditions [(a) addition of aldehyde **13ff** at −75 °C, or at −110 °C in the presence of 2-methylbutane; (b) transmetalation of the lithium enolate with 2 molar equiv of freshly prepared MgI_2 or $MgBr_2$] consistently gave **14ff** with 55–60% de, which was not significantly changed by recrystallization from warm acetone/hexane.

Methyl (3*S*)-Hydroxy-4-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]butanoate (15ff). Sodium (6.6 g, 287 mmol) was dissolved in CH_3OH (300 mL). This solution (271 mL, containing 260 mmol of $NaOCH_3$) was added dropwise within 10 min to a solution of **14ff** (520 mmol) in CH_3OH (2.5 L). The mixture was stirred for 90 min at ambient temperature. Glacial acetic acid (17.2 g, 286 mmol) was added dropwise with ice cooling. Solvents were removed in vacuo. The residue was redissolved in Et_2O and washed with 20% NaCl solution and then with saturated $NaHCO_3$ solution and with brine. The solution was dried ($MgSO_4$) and the solvent was evaporated in vacuo. *n*-Hexane (3 L) was added to the residue and the suspension was stirred extensively (90 min). The precipitated 1,1,2-triphenylethane-1,2-diol (150 g) was filtered off and washed with hexane. The filtrate was evaporated in vacuo to leave colorless crystals [192 g, 495 mmol, 95% yield, mp 72–74 °C, 65% ee (^1H NMR/Eu(hfc)$_3$]. A sample was dissolved in a small amount of warm methanol and kept in a freezer to give crystals that had mp 76–77 °C and 66% ee. Anal. ($C_{23}H_{29}FO_4$) C, H, F.

***tert*-Butyl (5*S*)-Hydroxy-3-oxo-6-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]hexanoate (16ff).** *tert*-Butyl acetate (232.4 g, 2.0 mol) was added dropwise at −70 °C under N_2 to a solution of LDA (2.05 mol) in THF/hexane (1:1, 2.5 L). After 1 h at −70 °C, the solution of methyl ester **15ff** (194 g, 0.5 mol) in THF (1.0 L) was added (10 min) and the mixture was stirred for 2.5 h at −20 °C. The cold yellow solution was poured into 20% aqueous NH_4Cl solution (5 L), leading to decolorization. The mixture was stirred for 10 min and then extracted with Et_2O (2 × 2 L). The extracts were washed with brine, saturated $NaHCO_3$ solution, and brine and dried ($MgSO_4$). The solvent was evaporated in vacuo to leave a pale-yellow oil (274 g, >100%) that slowly crystallized. A pure sample was obtained by chromatog-

(68) Commercially available from Aldrich Chemical Co.; Milwaukee, WI.

raphy (SiO_2, cyclohexane/EtOAc 3:1). Anal. ($C_{28}H_{37}FO_5$) C, H, F.

***tert*-Butyl 3(*R*),5(*S*)-Dihydroxy-6-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]hexanoate (10ff).** Triethylborane (560 mL of a 1 M solution in THF) was added dropwise at 20 °C to a solution of CH_3OH (375 mL) in THF (1.5 L). The solution was stirred for 1 h. It was cooled to −78 °C. A solution of crude *tert*-butyl ester **16ff** (236 g, 0.5 mol) in THF (800 mL) was added dropwise and the solution was stirred for 1 h at −70 to −75 °C. $NaBH_4$ (24.7 g, 0.65 mol) was added at once and stirring was continued for 3 h at this temperature. The cold mixture was poured into a 20% aqueous NH_4Cl solution (3 L) and extracted with Et_2O (3 × 1 L). The extracts were washed with brine and dried, and the solvent was evaporated in vacuo. The residual oil was redissolved several times in wet methanol and this solvent was evaporated in vacuo at <20 °C. A methanolic solution was allowed to stand at 0 °C overnight. TLC (toluene/Et_2O 6:1) indicated the successful conversion of the nonpolar boron ester of the diol to free diol **10ff** (R_f = 0.11). Pure **10ff** was obtained after chromatography through silica (3.6 kg) with toluene/Et_2O 6:1 as a colorless solid (175 g, 75% yield, mp 64–65 °C). Anal. ($C_{28}H_{39}FO_5$) C, H, F.

Sodium 3(*R*),5(*S*)-Dihydroxy-6-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]hexanoate (11ff). 1 N NaOH (245 mL) was added dropwise at 0–5 °C to a solution of *tert*-butyl ester **10ff** (118.5 g, 0.25 mol) in EtOH (300 mL). The solution was stirred for 4 h at 25 °C. Solvents were removed in vacuo. Toluene was added several times and the solvent was evaporated in vacuo each time. *n*-Pentane (1 L) was added and the suspension was stirred for 30 min. The solid was collected by suction filtration (88 g, 80% yield, mp 230–233 °C dec). Anal. ($C_{24}H_{30}FO_5Na$) C, H, F.

HPLC (Nucleosil 7 C_{18}, H_2O/CH_3CN 60:40 + 0.1% NH_4OAc, 40 °C, 1.0 mL/min, detect. 260 nm) indicated the presence of the title compound (94.9%, t_R 11.87 min, identical with material obtained from **10ff**) and a homogeneous, slightly more polar impurity (5.0%, t_R 10.00 min, most likely the 3(*S*) diastereomer of **11ff**, due to incomplete stereoselectivity of the $Et_3B/NaBH_4$ reduction). A 13-g portion (12% yield) of **11ff**, containing 8.0% of the (diastereomeric) impurity, was obtained from the mother liquor.

4(*R*)-Hydroxy-6(*S*)-[[2,4-diisopropyl-6-(4-fluorophenyl)-phenoxy]methyl]tetrahydro-2*H*-pyran-2-one (4ff), Prepared from Sodium Carboxylate 11ff According to Scheme II. 2 N hydrochloric acid (50 mL) was added at 0 °C to a solution of sodium carboxylate **11ff** (22.0 g, 50 mmol) in water (800 mL). The precipitated carboxylic acid was immediately extracted twice with EtOAc. The combined extracts were washed twice with brine and then dried and evaporated to dryness in vacuo. The residue was dried in vacuo (20.92 g, 50 mmol, mp 97–100 °C). It was dissolved in THF (250 mL) and NEt_3 (5.57 g, 55 mmol) was added at 0–5 °C. The mixture was stirred for 10 min at 0 °C and then cooled to −10 °C, and ethyl chloroformate (5.43 g, 50 mmol) was added dropwise. The mixture was stirred for 1 h at −5 °C. A 20% NaCl solution (1 L) was added. The solution was extracted with Et_2O (3 × 300 mL). The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was chromatographed with toluene/EtOAc 3:1 + 0.03% NEt_3 through silica (2 kg). Small nonpolar impurities were removed and the last product-containing fractions were cutoff to reduce the amount of diastereomer. The solvent was removed in vacuo, and the residue was washed with a small amount of cold Et_2O and then with *n*-pentane. The solid was dried in vacuo to give a colorless powder (13.7 g, 34.2 mmol, 68% yield, mp 142–144 °C). Anal. ($C_{24}H_{29}FO_4$) C, H, F.

HPLC (LiChrosorb SI 60 Merck, *n*-hexane/cyclohexane/1,2-dimethoxyethane 50:100:45, 40 °C, 1.0 mL/min, detect. 254 nm) indicated a chemical purity of the title compound (t_R 19.4 min) of 96.8%. The major impurity (t_R 22.95 min, probably 4(*S*)-hydroxy diastereomer) was 1.2%. For ^1H NMR determination of enantiomeric purity 2 × 5.5 mg of **11ff** was dissolved in CD_2Cl_2 in two NMR tubes. (+)-Eu(hfc)$_3$ (15 mg) and 25 mg of (−)-Eu(hfc)$_3$, respectively, were added, and the 400-MHz spectra were recorded. Sufficient differentiation of the signals of enantiomers were obtained for four sets of signals that in the absence of Eu(hfc)$_3$ were located at (1) δ = 7.50 ppm (2 H, AA′ part of AA′XX′Y, 2,6-H of FC_6H_4), (2) δ = 7.10 ppm (1 H, d, 3-H of 2-(4-FC_6H_5)-4,6-(*i*-Pr)$_2C_6H_2O$), (3) δ = 7.00 ppm (1 H, d, 5-H of 2-(4-FC_6H_5)-(4,6-*i*-Pr)$_2C_6H_2O$, (4) δ = ? (2 H, d with fine coupling, methylene group).

In the case of (+)-Eu(hfc)$_3$ signals of the minor enantiomer were shifted upfield relative to the corresponding signals of the major enantiomer. The indicated sets of signals (major/minor) were located at (1) δ = 8.58/8.51, (2) 7.58/7.53, (3) 7.48/7.43, (4) 6.16/6.06 ppm.

In the case of (−)-Eu(hfc)$_3$ signals of the minor enantiomer were shifted downfield relative to the corresponding signals of the major enantiomer. The indicated sets of signals (major/minor) were located at (1) δ = 8.54/8.62, (2) 7.55/7.59, (3) 7.45/7.49, (4) 6.18/6.26 ppm.

The ratio of integrals (major/minor, average from three recorded integrals) was 81:19 ± 3, regardless which of the indicated signal sets was used and regardless of the absolute configuration of Eu(hfc)$_3$. This corresponds to 62% ee of **11ff**.

2(*RS*)-Methoxy-4(*R*)-(*tert*-butyldiphenylsiloxy)-6(*S*)-[[(*p*-tolylsulfonyl)oxy]methyl]tetrahydropyran (21). *p*-Toluenesulfonyl chloride (112 g, 587 mmol) was added portionwise to a solution of alcohol **20**[32] (120 g, 300 mmol) in CH_2Cl_2 (0.5 L) and pyridine (0.5 L). The mixture was stirred for 3 h at ambient temperature. Solvents were removed in vacuo. The residue was redissolved in toluene and washed twice with water, twice with saturated $NaHCO_3$ solution, and once with brine. The organic phase was dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was chromatographed through silica (1.6 kg) with toluene/EtOAc 10:1. Unreacted *p*-TsCl was eluted first, followed by the title compound (163 g, yield 98%) as a nearly colorless glass.

2(*RS*)-Methoxy-4(*R*)-(*tert*-butyldiphenylsiloxy)-6(*S*)-(iodomethyl)tetrahydropyran (22). NaI (418 g, 2.79 mol) was added to the solution of tosylate **21** (193 g, 0.35 mol) in acetone (dried over K_2CO_3; 4.0 L). The mixture was refluxed for 24 h, allowed to cool, and filtered. The solvent of the filtrate was removed in vacuo. The residue was divided between Et_2O and water. The organic phase was washed with water, twice with 5% aqueous $NaHSO_3$ solution, with saturated $NaHCO_3$ solution, and then with water. It was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was chromatographed through silica (2.4 kg) with CH_2Cl_2. **22** was obtained (160 g, 90% yield) as a colorless glass. Anal. ($C_{23}H_{31}IO_3Si$) C, H, I.

Coupling of Phenols 8 with Iodide 22 To Give Lactol Ethers 23. Typical Procedure: 2(*RS*)-Methoxy-4(*R*)-[*tert*-butyldiphenylsiloxy]-6(*S*)-[[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]methyl]tetrahydropyran (23ff). Phenol **8ff** (27.2 g, 0.1 mol) was added to the suspension of K_2CO_3 powder (27.6 g, 0.2 mol) and hydroquinone (50 mg) in DMSO (250 mL). The mixture was stirred for 45 min at 25 °C. The solution of iodide **22** (61.1 g, 0.12 mol) in DMSO (250 mL) was added, and the mixture was stirred for 4 h at 50–55 °C. TLC (cyclohexane/EtOAc; first development 9:1, second development 15:1) indicated the complete disappearance of iodide **22** (R_f 0.51), but still some unreacted phenol **8ff** (R_f 0.71), besides the title compound **23ff** (R_f 0.61). The mixture was allowed to cool. A 20% NaCl solution (1 L) and Et_2O (1 L) were added. The organic phase was separated and the aqueous phase was extracted with Et_2O (3 × 500 mL). The combined extracts were washed with water (2 × 100 mL) and with brine and dried, and the solvent was evaporated in vacuo. The residue was chromatographed through silica (1.6 kg) first with cyclohexane/toluene 1:2, then toluene, and then toluene/EtOAc 30:1, to give **23ff** (51.0 g, 78% yield) as a colorless glass.

In analogous reactions **23a–p,g** (3 h, 70 °C), **23t–v,y–cc,ee** (1 h, 40 °C), **23gg** (8 h, 55 °C), and **23hh,oo** were obtained in 66–83% yield. **23mm,nn** (2 h, 50 °C) were obtained in 55–58% yield. **23dd** (5 h, 40 °C, careful O_2 exclusion) was obtained in 35% yield. **23pp** (1 h, 50 °C) was obtained in 65% yield.

2(*RS*)-Hydroxy-4(*R*)-[*tert*-butyldiphenylsiloxy]-6(*S*)-[[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]methyl]tetrahydropyran (24ff). A solution of **23ff** (50.0 g, 76.3 mmol) in THF (4.5 L), H_2O (4.5 L), and glacial acetic acid (6.3 L) was stirred for 26 h at 80–85 °C bath temperature. TLC (cyclohexane/EtOAc 9:1) indicated that only little unreacted **23ff** was left. The solvents were removed in vacuo. The residue was redissolved repeatedly

in toluene (3 × 2 L), and the solvent was removed in vacuo each time. The residue was chromatographed through silica (2 kg) with cyclohexane/EtOAc 12:1 to obtain **24ff** (42.2 g, 86% yield) as an amorphous, colorless powder. Anal. ($C_{40}H_{49}FO_4Si$) C, H, F.

In analogous reactions **24a–c** (3 days), **24f,g**, **24h,i** (3 days), and **24k–q,t–v,y,bb–ee,gg** were obtained in 60–80% yield. **24hh** and **24aa** (2 days, 75 °C bath) were obtained in 85 and 92% yield, respectively. **24d,e,j,z** were obtained in 33–50% yield besides 31–38% of the requisite unreacted educts **23**. **24mm–pp** were obtained in 55–65% yield (besides 10–25% of recovered educts **23**), when acetic acid was substituted by trifluoroacetic acid. A representative procedure is as follows: A solution of **23oo** (3.8 g, 6.15 mmol) in THF (80 mL), H_2O (40 mL), and CF_3CO_2H (40 mL) was stirred for 4 h at 60 °C. At 20 °C the pH was adjusted to 5.5 with 4 N NaOH (115 mL). The solvents were removed in vacuo, and the residue was extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was chromatographed through silica (200 g) with cyclohexane/EtOAc 2:1 to give **24oo** (2.2 g, 59% yield) as a colorless, amorphous solid.

Oxidation of Lactol 24 to Lactone 25 with *N*-Iodosuccinimide. Typical Procedure: 4(*R*)-(*tert*-Butyldiphenylsiloxy)-6(*S*)-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxymethyl]tetrahydropyran-2-one (25ff). Tetra-*n*-butylammonium iodide (19.25 g, 52.1 mmol) was added with cooling and stirring (10 °C) to the solution of lactol **24ff** (33.4 g, 52.1 mmol) in CH_2Cl_2 (2.5 L). *N*-iodosuccinimide (46.9 g, 208.4 mmol) was added. The mixture was stirred with exclusion of light (covered with alumina foil) for 1 h at 10 °C and 20 h at ambient temperature. TLC (cyclohexane/EtOAc 9:1) indicated complete disappearance of **24ff** (R_f 0.11) and the clean formation of the product (R_f 0.23). The mixture was washed with water (1 L), with 5% aqueous $NaHSO_3$ solution (3 × 1 L), and water (0.5 L). The organic phase was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was filtered through silica (2 kg) with cyclohexane/EtOAc 92:8, to obtain **25ff** (33.0 g, yield 99%) as a colorless glass. Anal. ($C_{40}H_{47}FO_4Si$) C, H, F.

In analogous reactions **25q,dd,ee,gg,hh,mm–pp** were obtained in 82–98% yield, generally as colorless, amorphous solids.

Oxidation of Lactol 24 to Lactone 25 with CrO_3 on Celite. Typical Procedure: 4(*R*)-[*tert*-Butyldiphenylsiloxy]-6-(*S*)-[[2,4-dichloro-6-(cyclohexylidenefluoromethyl)phenoxy]methyl]tetrahydropyran-2-one (25y). Powdered chromium trioxide (8.6 g, 86 mmol) was added at 15–20 °C to a suspension of Celite (5 g) in CH_2Cl_2 (100 mL). A solution of pyridine (13.6 g, 172 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was stirred for 20 min at 20–25 °C. A solution of lactol **24y** (5.7 g, 8.6 mmol) in CH_2Cl_2 (60 mL) was added dropwise. The suspension was stirred for 1 h at 20–25 °C. TLC indicated complete disappearance of **24y** and clean formation of the product. CH_2Cl_2 (400 mL) and Celite (100 g) was added and the mixture was suction filtered. The solid was washed with CH_2Cl_2 (100 mL). The combined filtrates were filtered through Celite again, and then the solvent was removed in vacuo. The residue was dissolved in a minimal amount of cyclohexane/EtOAc 1:1, given onto a column of silica (400 g), and flash chromatographed with cyclohexane/EtOAc 9:1. **25y** (5.0 g, yield 88%) was obtained as an amorphous colorless solid. Anal. ($C_{35}H_{40}Cl_2F_2SiO_4$) C, H, Cl.

In analogous reactions **25a–p,t–v,y–cc** were obtained in 82–90% yield, generally as colorless, amorphous solids.

Deprotection of β-Silyloxy Lactones 25 To Give β-Hydroxy Lactones 4. Typical Procedure: 4(*R*)-Hydroxy-6(*S*)-[[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]methyl]tetrahydropyran-2-one (4ff). Glacial acetic acid (11.65 g, 194.1 mmol), then tetra-*n*-butylammonium fluoride trihydrate (45.92 g, 145.6 mmol), was added at 20 °C to a stirred solution of **25** (31.0 g, 48.5 mmol) in THF (1.5 L). The mixture was stirred for 4 h at ambient temperature and then allowed to stand overnight. The solvent was removed in vacuo. Et_2O (1 L) and water (0.5 L) were added to the residue. The aqueous phase was extracted with Et_2O (2 × 0.5 L) and the combined ethereal solutions were washed with water (0.1 L) and brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was dissolved in toluene and the solvent was evaporated in vacuo. The residue was chromatographed through silica (2 kg) with cyclohexane/EtOAc 1:1 to give **4ff** (16.2 g, 83% yield) as colorless crystals (mp 145–146 °C). Anal. ($C_{24}H_{29}FO_4$) C, H, F.

For yields of other compounds of general formula **4**, obtained by analogous reactions, see Table I; for spectra, see Table X of the supplementary material. **4r** and **4s** were prepared according to another procedure (vide infra).

Saponification of β-Hydroxy Lactones 4 To Give β,δ-Dihydroxy Sodium Carboxylates 11. Typical Procedure: Sodium 3(*R*),5(*S*)-Dihydroxy-6-[2,4-diisopropyl-6-(4-fluorophenyl)phenoxy]hexanoate (11ff). Aqueous NaOH (1 N, 18.4 mL, 18.4 mmol) was added dropwise at 10 °C to a solution of **4ff** (7.0 g, 17.5 mmol) in EtOH (800 mL). The solution was stirred 1 h at 20–25 °C. TLC ($CHCl_3/CH_3OH$ 8:2) indicated complete disappearance of **11ff** and a homogeneous product (R_f 0.26). The solvent was removed in vacuo. The residue was dissolved in ethanol and the solvent was evaporated in vacuo. The residue was stirred for 10 min in *n*-pentane (50 mL) and then suction filtered, and the washing was repeated. The solid was dried in vacuo to obtain **11ff** (7.2 g, 94% yield) as a colorless amorphous powder (mp 243–245 °C dec). Anal. ($C_{24}H_{30}FO_5Na$) C, H, F. HPLC (vide supra) indicated a purity of >99.5%.

For other compounds of general formula **11**, see Table I; for spectra, see Table X (supplementary material).

Preparation of *o*-Benzoylphenols 27 by Fries Rearrangement. Typical Procedure: 1-[(4-Fluorobenzoyl)oxy]-2,4-dichlorobenzene (26b). 2,4-Dichlorophenol (350 g, 2.16 mol) was added dropwise at 20 °C to the solution of NaOH (109.2 g, 2.72 mol) in H_2O (0.94 L). The mixture was stirred for 30 min. At 15–25 °C (cooling) 4-fluorobenzoyl chloride (500 g, 3.16 mol) was added dropwise. The mixture was stirred for 30 min at ambient temperature. TLC indicated quantitative disappearance of starting materials. The mixture was diluted with H_2O (2 L). The solid was filtered and washed with cold 10% aqueous NaOH solution (2 L) and then with H_2O (2 × 2 L). The solid was suspended in EtOH (2 L), stirred for 30 min, suction-filtered, washed with EtOH, and dried in vacuo at 50 °C to give a colorless solid (608 g, 99% yield, mp 128–129 °C). Anal. ($C_{13}H_7Cl_2FO_2$) C, H, Cl, F.

2,4-Dichloro-6-(4-fluorobenzoyl)phenol (27b). Ester **26b** (608 g, 2.14 mol) and $AlCl_3$ (712 g, 5.35 mol) were well mixed and slowly heated to 150 °C (inner temperature). The mixture was stirred for 2 h. TLC ($CHCl_3$) indicated disappearance of **26b**. The mixture was allowed to stand at 25 °C overnight. It was dissolved in EtOAc (4 L) with warming and then hydrolyzed at <30 °C (external cooling) with 2 N HCl (3 L). The organic phase was washed with 2 N HCl, with H_2O, and then with brine. It was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was suspended in *i*-Pr_2O (1 L) and stirred for 30 min. The solid was suction filtered, washed with *i*-Pr_2O, and dried in vacuo to give a slightly yellow solid (494 g, 81% yield, mp 120–123 °C). Anal. ($C_{13}H_7Cl_2FO_2$) C, H, Cl, F.

Preparation of 28 by Grignard Additions to *o*-Benzoylphenols 27. Typical Procedure: 2,4-Dichloro-6-[bis(4-fluorophenyl)hydroxymethyl]phenol (28b). (4-Fluorophenyl)magnesium bromide was prepared from Mg turnings (66.5 g, 2.77 mol) and 4-bromo-1-fluorobenzene (441 g, 2.52 mol) in THF (1.2 L). A solution of ketone **27b** (240 g, 0.845 mol) in THF (1 L) was added dropwise. The solvent was removed in vacuo. The residue was suspended in Et_2O (2.5 L) and 20% aqueous NH_4Cl solution (3 L) was added dropwise with cooling. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine and then dried, and the solvents were evaporated in vacuo. The residue was suspended in *i*-Pr_2O (1 L) and stirred for 15 min. The solid was suction filtered, washed with *i*-Pr_2O, and dried in vacuo to give slightly yellow crystals (273 g, 85% yield, mp 193–195 °C). Anal. ($C_{19}H_{12}Cl_2F_2O_2$) C, H, Cl, F.

Preparation of 8a–i by Hydrogenation of Benzylic Alcohols 28a–i. Typical Procedure: 2,4-Dichloro-6-[bis(4-fluorophenyl)methyl]phenol (8b). Benzylic alcohol **28b** (240 g, 0.632 mol) was dissolved in glacial acetic acid (4.8 L) and concentrated HCl (48 mL) with slight warming. After cooling to 20 °C, 10% Pd on charcoal (4 g) was added. The suspension was deoxygenated with N_2, then saturated with H_2, and hydrogenated at ambient temperature in a shaking device under 1 bar

of H_2. A 13.3-L portion of H_2 was consumed within 90 min. The catalyst was filtered off and washed with ethanol. The filtrates were concentrated in vacuo. The residue was dissolved in EtOAc (12 L) and washed with water, saturated $NaHCO_3$ solution, and brine. The organic phase was dried and the solvent was removed in vacuo to give an oil that was purified by chromatography through silica (6.4 kg) with cyclohexane/CH_2Cl_2 4:1 to give 170 g [74% yield, purity > 99.5% (GLC)]. Anal. ($C_{19}H_{12}Cl_2F_2O$) C, H, Cl, F.

Data for 8a–i may be obtained from Table XI of the supplementary material.

Preparation of Phenols 8j–o. Typical Procedure: 1-(4-Fluorophenyl)prop-2-en-1-ol. (4-Fluorophenyl)magnesium bromide was prepared from Mg turnings (13.3 g, 0.55 mol) and 4-bromo-1-fluorobenzene (87.5 g, 0.5 mol) in Et_2O (650 mL). The Grignard solution was cooled to −10 °C and the solution of acrolein (28 g, 0.5 mol) in Et_2O (100 mL) was added dropwise. The mixture was stirred for 1 h at −10 °C, and 20% aqueous NH_4Cl solution (0.5 L) was added dropwise. The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with water and dried, and the solvent was evaporated in vacuo. The residue was chromatographed through silica (1 kg) with CH_2Cl_2 to give the title compound (51 g, 67% yield).

1-(4-Fluorophenyl)-3-bromoprop-1-ene. A solution of PBr_3 (41.7 g, 154 mmol) in toluene (150 mL) was added dropwise at 0–5 °C to a solution of 1-(4-fluorophenyl)prop-2-en-1-ol (47 g, 309 mmol) in toluene (1.2 L). The mixture was washed twice with saturated $NaHCO_3$ solution and twice with brine. The organic solution was dried and the solvent was evaporated in vacuo. The residue was used immediately for the next step.

1-(4-Fluorophenyl)-3-(2,4-dichlorophenoxy)prop-1-ene (29j). 2,4-Dichlorophenol (50 g, 309 mmol) was added to crude 1-(4-fluorophenyl)-3-bromoprop-1-ene (309 mmol), followed by acetone (1 L) and K_2CO_3 (127 g, 927 mmol). The suspension was refluxed for 4 h. The solvent was removed in vacuo. The residue was dissolved in Et_2O, washed with H_2O, and dried, and the solvent was evaporated. The residue was recrystallized from hot petroleum ether, to give a colorless solid (72 g, 79% yield, mp 80–81 °C). Anal. ($C_{15}H_{11}Cl_2FO$) C, H, Cl, F.

2,4-Dichloro-6-[3-(4-fluorophenyl)prop-1-en-3-yl]phenol (30j). *N,N*-Dimethylaniline (38.1 g, 315 mmol) was added to a solution of **29j** (52.3 g, 210 mmol) in diethylene glycol monomethyl ether (600 mL). The mixture was heated for 10 h to 160 °C. It was allowed to cool. Et_2O (2 L) and petroleum ether (4 L) were added, and the solution was washed twice with 2 N HCl and twice with brine. It was dried, and the solvents were removed in vacuo. The residue was chromatographed through silica (1 kg) with cyclohexane/toluene 1:1 to give an oil (52.4 g, 84% yield).

1-(Benzyloxy)-2,4-dichloro-6-[3-(4-fluorophenyl)prop-1-en-3-yl]benzene (31j). K_2CO_3 (48.5 g, 351 mmol) and benzyl chloride (24.3 g, 192 mmol) were added to the solution of phenol **30j** (52.0 g, 175 mmol) in DMF (0.5 L). The suspension was heated for 8 h to 70–75 °C. Water (2 L) and Et_2O (2 L) were added to the cold suspension. The ether phase was washed twice with 2 N NaOH solution and twice with brine. It was dried, and the solvent was evaporated. An analytical sample was obtained by chromatography (cyclohexane/EtOAc 50:1) of a small portion. The crude product (69.7 g, 100% yield) did not exhibit any impurity on TLC and was used in the next step.

1-(Benzyloxy)-2,4-dichloro-6-[1-(4-fluorophenyl)-3-hydroxypropyl]benzene (32j). A solution of **31j** (69.0 g, 179 mmol) was added dropwise to a 0.5 M solution of 9-BBN in THF (525 mL, 262 mmol). The solution was stirred for 30 min at ambient temperature and 90 min under reflux. It was cooled to 5 °C, and EtOH (105 mL), followed by 2 N aqueous NaOH (173 mL), was added dropwise. The mixture was cooled, and 30% aqueous H_2O_2 (45.5 mL) was added dropwise at <30 °C. The mixture was refluxed for 1 h. Toluene (2 L) was added, and the solution was washed with ice/water (3 × 0.5 L) and with brine (0.5 L). The organic phase was dried; the solvents were evaporated in vacuo. The residue was chromatographed through silica (2 kg) with cyclohexane/EtOAc 85:15 to give a colorless glass (56.7 g, 79% yield).

1-(Benzyloxy)-2,4-dichloro-6-[1-(4-fluorophenyl)-3-(tosyloxy)-1-propyl]benzene (33j). *p*-Toluenesulfonyl chloride (38.2 g, 200 mmol) was added in portions at 0–5 °C to the solution of **32j** (56.7 g, 140 mmol) in CH_2Cl_2 (150 mL) and pyridine (150 mL). The mixture was stirred for 6 h at 20 °C and allowed to stand at −10 °C overnight. The solvents were evaporated in vacuo. The residue was dissolved in toluene (0.5 L) and washed with H_2O (2 × 200 mL), saturated $NaHCO_3$ solution (2 × 200 mL), and brine. The organic phase was dried, and the solvent was evaporated in vacuo. The residue was filtered through silica (1 kg) with CH_2Cl_2 to give a pale pink oil (71.3 g, 91% yield).

1-(Benzyloxy)-2,4-dichloro-6-[1-(4-fluorophenyl)-3-iodo-1-propyl]benzene (34j). NaI (47.9 g, 319 mmol) was added to the solution of tosylate **33j** (71.3 g, 128 mmol) in acetone (1 L). The mixture was refluxed for 4 h. The solvent was removed in vacuo. The residue was dissolved in toluene. The solution was washed twice with water, twice with $NaHSO_3$ solution, once with $NaHCO_3$ solution, and then with brine. The organic phase was dried, and the solvent was removed in vacuo. The residue was chromatographed through silica (1 kg) with cyclohexane/EtOAc 9:1 to give an oil (45.6 g, 70% yield).

1-(Benzyloxy)-2,4-dichloro-6-[1-(4-fluorophenyl)-3-(4-fluorophenoxy)-1-propyl]benzene. K_2CO_3 (12.1 g, 87.7 mmol) was added to the solution of 4-fluorophenol (4.9 g, 43.8 mmol) in DMSO (30 mL). A solution of iodide **34j** (15.0 g, 29.2 mmol) in DMSO (80 mL) was added at once. The mixture was heated for 4 h to 50 °C. It was cooled, and Et_2O (0.5 L) and water (0.5 L) were added. The water phase was separated and extracted with Et_2O again. The combined extracts were washed with H_2O (2 × 100 mL) and then dried ($MgSO_4$), and the solvent was evaporated in vacuo. The residue was chromatographed through silica to give a colorless solid (11.1 g, 76% yield).

2,4-Dichloro-6-[1-(4-fluorophenyl)-3-(4-fluorophenoxy)-1-propyl]phenol (8j). N_2 was bubbled through the solution of the benzyl ether (5.5 g, 11 mmol) in glacial acetic acid (560 mL) and concentrated HCl (5.5 mL). Pd (10%) on charcoal (1.5 g) was added. The suspension was saturated with H_2 and shaken under 1 bar of H_2 at ambient temperature. A 250-mL portion of H_2 was consumed within 20 min. TLC (cyclohexane/EtOAc 9:1) indicated complete transformation of starting material (R_f 0.50) to product (R_f 0.29). The mixture was purged with N_2. The catalyst was filtered off and washed with ethanol. The filtrates were concentrated in vacuo. Toluene was added, and the solvent was evaporated in vacuo. The residue was chromatographed through silica (450 g) with cyclohexane/EtOAc 92:8 to give a colorless solid (4.5 g, 99% yield). For data see Table XI of the supplementary material.

2-Methyl-6-[3-(4-fluorophenoxy)-1-propyl]phenol (8l). A solution of chlorophenol **8k** (240 mg, 0.82 mmol) in EtOAc (40 mL) was purged with N_2. Pd (10%) on charcoal (40 mg) was added, and the mixture was shaken for 12 h under 1 bar of H_2. A 20-mL portion of H_2 was consumed during this time. The catalyst was filtered off. The filtrate was concentrated in vacuo. The residue was dissolved in toluene, and the solvent was evaporated in vacuo. The residue was chromatographed through silica with cyclohexane/EtOAc 92:8 to give a colorless solid (153.5 mg, 72% yield).

In analogy, **8o** was obtained from chlorophenol **8n** in 94% yield.

2,4-Dimethyl-6-(cyclohexylcarbonyl)phenol (8ss). A solution of cyclohexanecarbonyl chloride (55 g, 375 mmol) in CH_2Cl_2 (25 mL) was added dropwise at 20 °C to 2,4-dimethylphenol (**35a**; 41.5 g, 340 mmol). The mixture was stirred for 1 h at 20 °C. Then it was warmed to 60 °C, while the CH_2Cl_2 distilled off. The residue was stirred for 30 min at 60 °C. TLC (100% toluene) indicated complete transformation of **35a** (R_f 0.14) to 1-[(cyclohexylcarbonyl)oxy]-2,4-dimethylbenzene (R_f 0.41). It was cooled to 10 °C. $AlCl_3$ (49 g, 367 mmol) was added. The mixture was heated for 1 h to 150 °C. TLC indicated complete transformation to **8ss** (R_f 0.53). The mixture was cooled and then dissolved in EtOAc (500 mL). Ice (200 g) and 4 N HCl (200 mL) was added. The organic phase was washed with 2 N HCl and saturated $KHCO_3$ solution and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was filtered through silica (700 g) with toluene/cyclohexane 1:1 to obtain a colorless oil (70.9 g) that was distilled in a Kugelrohr apparatus (110 °C/7 × 10^{-5} bar) to give a colorless oil (69.9 g, 89% yield). Anal. ($C_{15}H_{20}O_2$) C, H.

2,4-Dichloro-6-(cyclohexylcarbonyl)phenol (8p) [4 h, 150 °C, mp 103 °C (from CH_3OH), 32% yield] and **2-Methyl-4-**

chloro-6-(cyclohexylcarbonyl)phenol (8tt) (4 h, 150 °C, 69% yield) were obtained by analogous procedures.

2,4-Dimethyl-6-(cyclohexylhydroxymethyl)phenol (8q). A solution of $NaBH_4$ (3.3 g, 87.2 mmol) in water (15 mL) was added at 0 °C to the solution of ketone **8ss** (20.0 g, 86.2 mmol) in methanol (200 mL). The mixture was stirred for 30 min at 20 °C. TLC (cyclohexane/EtOAc 4:1) indicated complete transformation of **8ss** into alcohol **8q**. The solvents were removed in vacuo. Water (15 mL) was added dropwise. The pH was adjusted to 4.0 with aqueous $NaHSO_4$ solution. The mixture was extracted four times with CH_2Cl_2. The combined extracts were dried (Na_2SO_4), and the solvents were removed in vacuo. The residue was filtered through silica with toluene/EtOAc 20:1. The eluent was removed in vacuo and the residue was recrystallized from *n*-hexane to obtain pale-yellow crystals (17.7 g, 88% yield, mp 116 °C). Anal. ($C_{15}H_{22}O_2$) C, H.

4(*R*)-(*tert*-Butyldiphenylsiloxy)-6(*S*)-[[2,4-dimethyl-6-(cyclohexylhydroxymethyl)phenoxy]methyl]tetrahydropyran-2-one (25q). **23q** (74% yield) and **24q** (76% yield) were obtained according to the typical procedures given above. Lactone **25q** (82% yield) was obtained, utilizing *N*-iodosuccinimide, according to the typical procedure. The two diastereomers of **25q** (stereochemistry of hydroxy group) can be separated by silica chromatography (toluene/EtOAc 95:5) under flash chromatography or, better yet, HPLC conditions. The R_f value of the *R* diastereomer is small than that of the *S* diastereomer.

4(*R*)-(*tert*-Butyldiphenylsiloxy)-6(*S*)-[[2,4-dimethyl-6-[cyclohexyl[(α,α-dimethylbutanoyl)oxy]methyl]phenoxy]methyl]tetrahydropyran-2-one (25r) and (25s). A solution of **25q** (*S* isomer; 350 mg, 0.58 mmol), α,α-dimethylbutanoic anhydride (310 mg, 1.45 mmol), and 4-(dimethylamino)pyridine (180 mg, 1.47 mmol) in toluene (10 mL) was heated for 48 h to 110 °C. The solvent was evaporated in vacuo. Further volatile components were removed (30 min) in a Kugelrohr distillation apparatus (60 °C/7 × 10^{-5} bar). The residue was purified by silica chromatography to give **25r** (260 mg, 65% yield) as a colorless glass.

In analogy, **25q** (*R* isomer, 293 mg) gave **25s** (236 mg, 69% yield) as a colorless glass.

4(*R*)-Hydroxy-6(*S*)-[[2,4-dimethyl-6-[cyclohexyl[(α,α-dimethylbutanoyl)oxy]methyl]phenoxy]methyl]tetrahydropyran-2-one (4r) and (4s). A solution of **25r** (250 mg, 0.36 mmol), α,α-dimethylbutanoic acid (90 mg, 0.77 mmol), and tetra-*n*-butylammonium fluoride trihydrate (600 mg, 1.90 mmol) in THF (20 mL) was kept at 0 °C for 16 h. Toluene (50 mL) was added, and the solvents were removed in vacuo. The residue was dissolved in a small amount of CH_2Cl_2 and chromatographed through silica gel with cyclohexane/EtOAc 2:1. Toluene was added to the pure product, and the solvent was evaporated in vacuo. The residue was dried in vacuo to obtain **4r** (145 mg, 90% yield) as a colorless glass. Anal. ($C_{27}H_{40}O_6$) C, H.

In analogy, from **25s** (230 mg) there was obtained **4s** (140 mg). For spectra of **4r** and **4s**, see Table X of the supplementary material.

Preparation of Phenols 8t–v by Reduction of Phenolic Ketones. Typical Procedure: 2,4-Dichloro-6-(cyclohexylmethyl)phenol (8u). A solution of $NaBH_4$ (5.8 g, 153 mmol) in ice/water (50 mL) was added dropwise at 0 °C to the solution of ketone **8p** (55.7 g 204 mmol) in CH_3OH (1 L). The mixture was stirred for 1 h at 20 °C. Solvents were removed in vacuo. Et_2O (100 mL) was added. 2 N H_2SO_4 was added at 10 °C until the pH remained acidic. The organic phase was separated, and the aqueous phase was extracted twice with ether. The combined organic phases were dried ($MgSO_4$), and the solvent was removed in vacuo to leave a semisolid [55.2 g, crude 2,4-dichloro-6-cyclohexylhydroxymethyl)phenol (**8uu**)].

A solution of $AlCl_3$ (189 g, 1.42 mol) in Et_2O (270 mL) was added at 0 °C to the suspension of $LiAlH_4$ (26.8 g, 0.71 mol) in Et_2O (270 mL). A solution of crude alcohol **8uu** (55.2 g, 0.20 mol) in Et_2O (170 mL) was added dropwise. The mixture was purged with N_2, and the reaction temperature was raised to 80 °C, while the Et_2O was distilling off. After 15 min at 80 °C gas evolution started and ceased after 30 min. The mixture was stirred for 15 additional minutes at 80 °C. It was cooled and Et_2O (500 mL) was added. At 0 °C 1 N HCl (500 mL) was added dropwise (**caution**! highly exothermic, H_2 evolution). The organic phase was separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed with 2 N HCl and with brine. They were dried, and the solvent was evaporated in vacuo. The residue was chromatographed through silica first with cyclohexane/toluene 1:1, then with toluene, and then with toluene/EtOAc 9:1 to give **8u** (40.7 g, 77% yield) as a glass and unreacted alcohol **8uu** (6.5 g, 12%) as a solid (mp 86 °C from *n*-pentane). **8u** was distilled in a Kugelrohr apparatus (100 °C/7 × 10^{-4} bar) to get a colorless solid (40.0 g, mp 45 °C). Anal. ($C_{13}H_{16}Cl_2O$) C, H, Cl.

8t and **8y** were obtained in 65 and 48% yield, respectively, when the ketones were subjected immediately to the $LiAlH_4/AlCl_3$ reduction, the prior reduction of ketone to alcohol being unnecessary. This shortened procedure with **8p** gave alcohol **8uu** and less than 10% of **8u**.

4(*R*)-(*tert*-Butyldiphenylsiloxy)-6(*S*)-[[2,4-dimethyl-6-[cyclohexyl(1,1-dimethylpropanamido)methyl]phenoxy]methyl]tetrahydropyran-2-one (25w and 25x). A solution of alcohol **25q** (1:1 mixture of diastereomers, 1.06 g, 1.77 mmol) in α,α-dimethylbutyronitrile (10 mL) and 48% aqueous HF (1 mL) was stirred for 50 h at 25 °C. TLC (cyclohexane/EtOAc 4:1) indicated clean transformation of **25q** (R_f 0.18) to **25w** (R_f 0.32) and **25x** (R_f 0.25). CH_2Cl_2 (40 mL) and aqueous $KHCO_3$ solution (10 mL) were added. The organic phase was separated and dried ($MgSO_4$), and the solvents and excess reagent (bp 128–129 °C) were removed in vacuo. HPLC (silica, cyclohexane/EtOAc 20:1) gave **25w** (546 mg) and **25x** (490 mg) as colorless solids.

β-Silyloxy lactones **25w** and **25x** were deprotected to give **4w** and **4x**, respectively, according to the typical procedure and Table I.

2,4-Dichloro-6-(cyclohexylidenefluoromethyl)phenol (8y). DAST (9.66 g, 7.9 mL, 60 mmol) was added dropwise with a syringe at 0–5 °C to a solution of ketone **8p** (10.8 g, 40 mmol) in toluene (60 mL). The mixture was stirred for 2 h at 25 °C. It was added dropwise at 0 °C into a stirred two-phase mixture of toluene (200 mL) and saturated Na_2CO_3 solution (200 mL). The mixture was stirred for 20 min. The organic phase was separated, and the aqueous layer was extracted with toluene again. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. The residue was chromatographed through silica (500 g) with cyclohexane/toluene 3:1 to give **8y** (5.1 g, yield 47%) and recovered **8p** (2.8 g, 26%). **8y**: Anal. ($C_{13}H_{13}Cl_2FO$) C, H, Cl.

2,4-Dimethyl-6-[cyclohexylidene(4-fluorophenyl)methyl]phenol (36). To a Grignard solution, prepared from cyclohexyl chloride (7.15 g, 60.3 mmol) and Mg turnings (1.6 g, 65.8 mmol) in Et_2O (100 mL) (20-min reflux) was added dropwise a solution of 2,4-dimethyl-6-[(4-fluorophenyl)carbonyl]phenol (4.9 g, 20.1 mmol) in Et_2O (50 mL). The mixture was stirred for 3 h at 20 °C. HCl (2 N, 40 mL) was added dropwise. The aqueous phase was extracted with Et_2O (2 × 100 mL). The combined Et_2O layers were washed with brine and dried, and the solvent was evaporated. The residue was dissolved in toluene (50 mL). *p*-Toluenesulfonic acid (100 mg) was added, and the mixture was warmed for 2 h to 100 °C. The main product was purified by silica chromatography (cyclohexane) and then Kugelrohr distilled (~130 °C/7 × 10^{-5} bar) to give a solid (4.4 g, 70% yield).

2,4-Dimethyl-6-[cyclohexyl(4-fluorophenyl)methyl]phenol (8z). A solution of **36** (1.8 g) in CH_3OH, containing 10% Pd/C (0.5 g) was shaken for 5 h under 1 bar of H_2. Standard workup gave an oil that was purified by Kugelrohr distillation (~150 °C/1 × 10^{-4} bar) to give 1.6 g (89% yield) of an oil that slowly crystallized. Anal. ($C_{21}H_{25}FO$) C, H, F.

3-Isopropyl-4-nitrobiphenyl (38). A 0.7 M solution of isopropylmagnesium chloride in THF (343 mL, 240 mmol) was added at −70 °C within 3 h to the solution of 4-nitrobiphenyl (**37**; 20 g, 100 mmol) in THF (400 mL). The mixture was stirred for 1 h at −70 °C. 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ; 22.7 g, 100 mmol) was added at once at −40 °C. The mixture was allowed to warm to 20 °C and was stirred for 1 h at this temperature. The reaction mixture was poured into H_2O (1.2 L) and allowed to stand overnight. The organic solvent was removed in vacuo. The aqueous phase was extracted with EtOAc (3 × 0.5 L). The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. The residue (21 g) was chromatographed through silica with cyclohexane/CH_2Cl_2 4:1 to

give a pale-red oil (7.9 g, 33% yield).

3-(Cyclohexylmethyl)-5-isopropyl-4-nitrobiphenyl (39). A Grignard solution was prepared from cyclohexylmethyl bromide (4.1 g, 23.2 mmol), Mg turnings (564 mg, 23.2 mmol), and THF (30 mL). This solution was added dropwise at −70 °C within 45 min to a solution of **38** (2.8 g, 11.6 mmol) in THF (30 mL). At −40 °C DDQ (5.27 g, 23.2 mmol) was added at once. The mixture was stirred for 90 min at 20 °C. Toluene and H_2O was added. After 20 min the aqueous phase was separated and washed with toluene. The combined toluene layers were washed with H_2O and dried, and the solvent was evaporated in vacuo. The residue (6.2 g) was chromatographed through silica with cyclohexane/toluene 9:1 to give a pale-red oil (2.0 g, 51% yield).

3-(Cyclohexylmethyl)-5-isopropyl-4-aminobiphenyl (40). Nitro compound **39** (1.95 g, 5.78 mmol) was dissolved in a methanolic solution (150 mL) of ammonia (20 g/L). Raney Ni (3 g) was added, and the mixture was shaken for 2 h at 20 °C in a H_2 atmosphere. The catalyst was filtered off and washed with CH_3OH. The filtrate was evaporated in vacuo. The residue was chromatographed (cyclohexane/toluene 1:2) to give a colorless oil (1.62 g, 91% yield).

2-(Cyclohexylmethyl)-4-phenyl-6-isopropylphenol (8aa). A suspension of amine **40** (1.6 g, 5.2 mmol) in hot 20% aqueous hydrobromic acid (10 mL) was quickly cooled to 0 °C with extensive stirring. The solution of $NaNO_2$ (450 mg, 6.5 mmol) in H_2O (1.5 mL) was added dropwise. The mixture was stirred for 15 min at 0 °C. Urea (90 mg, 1.5 mmol) was added, and the mixture was stirred for 10 min at 0 °C and then heated to 100 °C, until the N_2 evolution ceased (1 h). Et_2O (50 mL) and brine (20 mL) were added. The aqueous phase was extracted with Et_2O again. The combined ethereal phases were washed with saturated $NaHCO_3$ solution and then with brine and dried, and the solvent was evaporated. The residue was filtered through silica with cyclohexane/toluene 7:3 to give **8aa** (810 mg, yield 50%) as a colorless oil that slowly crystallized. Anal. ($C_{22}H_{28}O$) C, H.

3,5-Dichloro-2-hydroxybiphenyl (8bb). Chlorine was bubbled for 3 h at 20 °C into a solution of 2-hydroxybiphenyl (**41**, 17.0 g, 0.1 mol) in glacial acetic acid (50 mL). TLC (toluene/cyclohexane 7:3) indicated quantitative conversion of the starting material (R_f 0.18) to the product **8bb** (R_f 0.42) and a minor byproduct (R_f 0.53). The reaction mixture was poured onto ice (500 g) and extracted with Et_2O (3 × 100 mL). The combined extracts were dried, and the solvent was evaporated in vacuo. The residue was dissolved in toluene (2 × 100 mL) and the solvent was evaporated in vacuo each time. The residue was chromatographed through silica (1.8 kg) with cyclohexane/toluene 1:1 (5 L) to obtain pure **8bb** (21.57 g, 90% yield). Anal. ($C_{12}H_8Cl_2O$) C, H, Cl.

2,4-Dichloro-5-[(4-fluorobenzyl)oxy]phenol (8cc). A solution of 4,6-dichlororesorcine (**42**; 17.9 g, 0.1 mol), NaOH pellets (4.0 g, 0.1 mol), and 4-fluorobenzyl bromide (18.9, 0.1 mol) in DMF (50 mL) was heated for 4 h to 100 °C. The mixture was cooled, and H_2O (150 mL) was added. The mixture was acidified and then extracted with Et_2O (2 × 100 mL). The extracts were washed with water and with brine and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was recrystallized with charcoal from cyclohexane/i-Pr_2O to give a colorless solid (8.3 g) that after Kugelrohr distillation (190 °C/7 × 10^{-5} bar) had mp 105 °C. This solid was 1,3-bis[(4-fluorobenzyl)oxy]-4,6-dichlorophenol. The mother liquor was chromatographed through silica with toluene to give **8cc** (4.8 g, 17% yield) as a colorless solid that after recrystallization from hot cyclohexane had mp 75 °C. Anal. ($C_{13}H_9Cl_2FO_2$) C, H, Cl.

γ-[Bis(4-fluorophenyl)hydroxymethyl]-β-naphthol (44). A Grignard solution was prepared from 4-bromofluorobenzene (140 g, 0.8 mol) and Mg turnings (21.1 g, 0.88 mol) in THF (600 mL) (60 °C, 90 min). The solution of 2-hydroxy-3-naphthoic acid methyl ester (**43**; 40.4 g, 0.2 mol) in THF (250 mL) was added dropwise to the Grignard solution. The mixture was stirred for 30 min at ambient temperature. The solvent was evaporated in vacuo. Et_2O (1 L) was added to the residue, followed by 20% aqueous NH_4Cl solution (0.5 L). The aqueous phase was extracted with ether (0.5 L). The combined ethereal phases were washed with water and with brine, dried, and evaporated. The residual oil was dissolved at 25 °C in i-Pr_2O. The same volume of n-pentane was added. The precipitate was suction filtered and washed with n-pentane to give **44** (45 g, mp 173–175 °C). Additional **44** (5.5 g, mp 171–173 °C) was obtained from the mother liquor (total yield 50.5 g, 70%).

γ-[Bis(4-fluorophenyl)methyl]-β-naphthol (45). A solution of **44** (50 g, 138 mmol) in AcOH (1.2 L) and concentrated HCl (12 mL) was purged with N_2. Pd (10%) on charcoal (4 g) was added and the mixture was shaken under 1 bar of H_2 at 25 °C until H_2 uptake ceased (3.6 L). The catalyst was filtered off and the filtrate was evaporated in vacuo. The residue was dissolved in toluene (0.5 L) and washed with H_2O (2 × 0.25 L), with saturated $NaHCO_3$ solution (0.25 L), and with brine. The organic solution was dried and evaporated in vacuo. The residue was chromatographed through silica (2 kg) with cyclohexane/CH_2Cl_2 1:1 to give a very thick oil (39.3 g, yield 82%) that slowly crystallized.

α-Formyl-γ-[bis(4-fluorophenyl)methyl]-β-naphthol (46). A solution of NaOH (12.8 g, 320 mmol) in H_2O (27 mL) was added dropwise to a solution of **45** (8.0 g, 23.1 mmol) in EtOH (70 mL). The mixture was heated to 70–80 °C and $CHCl_3$ (8.8 g, 74 mmol) was added dropwise within 80 min. The mixture was stirred for 1 h at 80 °C. The solvent was removed in vacuo. H_2O (100 mL) was added, hydrochloric acid was added to pH 6, and the mixture was extracted with Et_2O (3 × 100 mL). The extracts were washed with water, dried, and evaporated in vacuo. The residue was chromatographed through silica (0.5 kg) with cyclohexane/EtOAc 93:7 to give a colorless solid (2.9 g, 34% yield), mp 137–139 °C) and recovered **45** (1.4 g).

2-Isopropyl-4-[bis(4-fluorophenyl)methyl]-β-naphthol (8dd). A solution of **45** (4.26 g, 12.3 mmol) in CH_3OH (15 mL) was added to a solution of Na (282 mg, 12.3 mmol) in CH_3OH (15 mL). The solvents were evaporated. Toluene (3 × 20 mL) was added to the residue and evaporated to dryness each time. The residue was dried for 1 h in vacuo. The solid was suspended in degassed toluene (50 mL) and heated to reflux with careful O_2 exclusion (argon). 2-Bromopropane (6.2 g, 50.4 mmol) was added dropwise within 30 min. The mixture was refluxed for 24 h. The cold mixture was acidified with 2 N HCl. H_2O (50 mL) was added. The organic layer was washed with brine and dried, and the solvent was evaporated in vacuo. All workup steps were performed quickly, minimizing O_2 contact. The residue was chromatographed through silica (300 g) with cyclohexane/EtOAc 93:7 to give **8dd** (3.7 g, 77% yield). Anal. ($C_{26}H_{22}F_2O$) C, H, F.

2-Methyl-4-[bis(4-fluorophenyl)methyl]-β-naphthol (8ee). A 70% (3.5 M) solution of sodium bis(2-methoxyethoxy)dihydroaluminate (Red-Al) in toluene (6.95 mL, 24.3 mmol) was diluted with xylene (20 mL). This solution was added at 120 °C to the solution of aldehyde **46** (2.6 g, 6.95 mmol) in xylene (100 mL), while the toluene was distilling off. When the reaction temperature reached 135 °C, the distillation head was replaced by a reflux condenser. After 2 h at reflux, the mixture was cooled, diluted with Et_2O (300 mL), and acidified with 20% aqueous H_2SO_4. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed twice with saturated $NaHCO_3$ solution and then with brine. They were dried, and the solvent was evaporated in vacuo. The residue was chromatographed through silica (100 g) with cyclohexane/toluene 1:1 to give **8ee** (1.3 g, yield 52%). Anal. ($C_{24}H_{18}F_2O$) C, H, F.

4-Acetoxy-3-(p-fluorophenyl)-2,5,6-triisopropylphenol (8kk). A solution of triethylamine (1.3 mL) and 4-(dimethylamino)pyridine (60 mg) in CH_2Cl_2 (5 mL) was purged with N_2. Substituted hydroquinone **61**[43] (1.55 g, 4.7 mmol) was added, and air contact was minimized. Acetic anhydride (0.62 g, 6.1 mmol, 1.3 equiv) was purged with N_2 and then added to the reaction mixture at −30 °C. The mixture was covered with argon, stoppered, and kept for 3 days in a freezer (−18 °C). The mixture was poured into ice/hydrochloric acid. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ solution and with brine. They were dried, and the solvent was removed in vacuo. The residue was chromatographed through silica (150 g) with cyclohexane/toluene 1:1, then with toluene. A colorless solid was obtained. (Mp 192–194 °C, 1.24 g, 70% yield). Anal. ($C_{23}H_{29}FO_3$) C, H, F.

1,4-Diacetoxy-6-(p-fluorophenyl)-2,3,5-triisopropylbenzene (62). Acetic anhydride (3.5 mL, 36.7 mmol, 3.0 equiv) and then pyridine (23 mL) were added at 0 °C to the substituted hydroquinone **61**[43] (4.04 g, 12.23 mmol). Reaction was conducted and worked up, and the product was isolated as described for **8kk** (vide

supra). A colorless solid was obtained. (Mp 172–173 °C, 3.06 g, 67% yield).

4-Acetoxy-6-(*p*-fluorophenyl)-2,3,5-triisopropylphenol (8ll). A solution of lithium hydroxide (114 mg, 4.77 mmol, 1.1 equiv) in water (10 mL) was added to a solution of diacetate **62** (1.8 g, 4.34 mmol) in 1,2-dimethoxyethane (30 mL). The mixture was stirred for 3 days at 25 °C. It was poured into 2 N HCl and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution and with brine and then dried and concentrated in vacuo. Column chromatography (conditions as with **8kk**) gave a colorless solid (mp 174–177 °C, 980 mg, 61% yield), besides **8kk** (480 mg, 30% yield). Anal. ($C_{23}H_{29}FO_3$) C, H, F.

***p*-Fluorophenacyl Acetate (63).** Bromine (25.7 mL, 0.5 mol) was added dropwise at 0 °C to the solution of *p*-fluoroacetophenone (69.1 g, 0.5 mol) in Et_2O (200 mL). After a short induction period, the bromine drops were immediately decolorized to give a pale yellow solution. It was washed with water and dried, and the solvent was evaporated to give an oil (97.0 g, 89% yield) that quickly crystallized. This crude compound was added to a suspension of sodium acetate (123.0 g, 1.5 mol) in glacial acetic acid (0.5 L). The mixture was warmed at 120 °C bath temperature under a reflux condenser to give a clear, colorless solution. After 1 h a colorless precipitate was observed. After 4 h at 120 °C the solvent was removed in vacuo (bath 60 °C). The residue was triturated with Et_2O (3 × 300 mL) and suction filtered each time. The combined filtrates were washed with saturated $NaHCO_3$ solution (6 × 100 mL) and then with brine. The solution was dried, and the solvent was evaporated. The residue (yellow solid) was distilled through a 15-cm Vigreux column in vacuo. After a prerun (bp 30–90 °C/1.3 × 10^{-4} bar, 4.6 g, yellow oil) there was obtained a colorless oil (bp 91–95 °C/9 × 10^{-5} bar, 76.6 g, 71% yield) that crystallized on standing.

2-(4-Fluorophenyl)-3-hydroxyquinoline-4-carboxylic Acid (64). KOH solution (6 N, 300 mL) was added to a solution of isatine (62 g, 0.42 mol) in EtOH (180 mL). The dark solution was heated to reflux, and a solution of *p*-fluorophenacyl acetate (**63**) (76 g, 0.387 mol) in EtOH (250-mL) was added dropwise within 30 min. The solution was refluxed for 12 h (bath 90 °C). Then most of the solvent (500 mL) was distilled off (bath 120 °C). The residue was poured into ice (1.8 kg)/concentrated HCl (480 mL). The yellow solid was suction filtered, suspended in hot 70% aqueous EtOH (4 L) and allowed to cool. The golden-yellow solid was suction filtered and dried at 50 °C in vacuo to give crude **64** (88.6 g, 81% yield, mp 206–207 °C dec). This crude product may be further purified via the sodium salt: saturated $NaHCO_3$ solution (500 mL) was added to the solution of crude **64** (14.2 g, 50 mmol) in EtOAc (250 mL). The mixture was stirred for 2 h at 20 °C. The organic layer was washed with brine and dried, and the solvent was evaporated in vacuo. The residue was recrystallized from CH_3OH to give a solid (15 g, 98% yield, mp 255 °C dec). This compound was pure by TLC and ^1H NMR.

2-(4-Fluorophenyl)-3-hydroxy-4-(methoxycarbonyl)-quinoline (65). An ethereal solution of diazomethane (30 mmol) was added at 0 °C to the suspension of crude, finely ground acid **64** (7.1 g, 25 mmol) in CH_2Cl_2 (0.5 L). The mixture was stirred for 30 min at 0 °C. The excess of CH_2N_2 was destroyed with some drops of acetic acid. Volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and then with water. The organic layer was dried and the solvent was evaporated in vacuo. The residue was chromatographed through silica with toluene/cyclohexane 4:1 to give a crystalline solid (6.0 g, 80% yield, mp 118–120 °C). Anal. ($C_{17}H_{12}FNO_3$) C, H, F, N.

2-(4-Fluorophenyl)-3-hydroxy-4-(hydroxymethyl)-quinoline (66). A solution of methyl ester **65** (14.86 g, 50 mmol) in Et_2O (150 mL) was added dropwise at 0–10 °C to the suspension of $LiAlH_4$ (1.9 g, 50 mmol) in Et_2O (150 mL). The mixture was stirred for 30 min, refluxed for 2 h, EtOAc (20 mL) and then H_2O (10 mL) were added, and then 2 N NaOH solution was added dropwise at 0 °C. EtOAc (50 mL) was added, and the mixture was filtered. The organic phase was dried and then evaporated in vacuo. The residue was chromatographed through silica with EtOAc/cyclohexane 1:2 to give a solid (9.3 g, 69% yield, mp 182–184 °C dec).

2-(4-Fluorophenyl)-3-hydroxy-4-methylquinoline (8mm). A solution of alcohol **66** (3.4 g, 12.6 mmol) in glacial acetic acid (500 mL) and concentrated hydrochloric acid (75 mL) was purged with N_2. Pd (10%) on charcoal (3.0 g) was added, and the mixture was shaken for 1 day under 1 bar of H_2. The catalyst was filtered off and washed with acetic acid. The filtrate was evaporated in vacuo. EtOAc and $NaHCO_3$ solution were added. The organic phase was separated and washed with brine, dried, and evaporated in vacuo. The residue was chromatographed (EtOAc/cyclohexane 1:4) to give a solid (2.2 g, 69% yield, mp 172–174 °C). Anal. ($C_{16}H_{12}FNO$) C, H, F, N.

2-(4-Fluorophenyl)-3-hydroxy-4-(2-hydroxy-2-propyl)-quinoline (67). A solution of **65** (4.46 g, 15 mmol) in THF (40 mL) was added dropwise at 35 °C to a Grignard reagent, prepared from Mg turnings (2.0 g, 82 mmol) and methyl iodide (10.65 g, 75 mmol) in Et_2O (60 mL). The mixture was stirred for 2 h at ambient temperature and then poured into 20% aqueous solution of NH_4Cl. The organic phase was separated and the aqueous phase was extracted twice with Et_2O. The combined organic phases were washed with water and then with brine and then dried. The solvent was evaporated in vacuo and the residue was chromatographed through silica (EtOAc/cyclohexane 1:4) to give a solid (4.0 g, 90% yield, mp 180–182 °C).

2-(4-Fluorophenyl)-3-hydroxy-4-isopropylquinoline (8nn). A solution of alcohol **67** (3.8 g, 12.8 mmol) and red phosphorus (3.97 g, 128 mmol, 10 equiv) in 67% aqueous HI (75 mL) was heated for 4 h at 150 °C (bath temperature). Volatiles were removed in vacuo. EtOAc and saturated $NaHCO_3$ was added to the residue. The aqueous phase was extracted with EtOAc. The combined EtOAc phases were washed with aqueous $NaHSO_3$ solution and with brine and then dried. The solvent was evaporated in vacuo and the residue was chromatographed through silica (EtOAc/cyclohexane 8:1) to give a solid (2.33 g, 65% yield, mp 173–175 °C). Anal. ($C_{18}H_{16}FNO$) C, H, F, N.

3-Hydroxy-2-methyl-4-phenylquinoline (8oo). Glacial acetic acid (100 mL), water (20 mL), and concentrated H_2SO_4 (1 mL) were added to the mixture of *o*-aminobenzophenone (**68**; 19.7 g, 0.1 mol) and hydroxyacetone (technical grade, Aldrich; 7.41 g, 6.85 mL, 0.1 mol). The mixture was refluxed for 4 h and allowed to stand at ambient temperature under N_2 overnight. The mixture was poured into ice-cold 10% NaOH solution (800 mL). The red brown solution was washed with Et_2O (5 × 100 mL). The aqueous phase (10–20%) was evaporated in vacuo to remove the small amount of dissolved Et_2O. The aqueous phase was acidified (AcOH) and allowed to stand at 0 °C until the precipitation was complete. The fine solid was suction filtered, washed with Et_2O, and dried in vacuo to obtain an ockre solid [21.9 g, 93% yield, mp 237–238 °C dec (lit.[56] mp 236–237 °C dec, 51% yield)].

***O*-[4,6-Dichloro-2-[bis(4-fluorophenyl)methyl]phenyl] *N,N*-Dimethylthiocarbamate (69).** Phenol **8b** (29.2 g, 80 mmol, 1 equiv) was given portionwise at 0 °C to the suspension of a 50% dispersion of sodium hydride in mineral oil (3.6 g) in DMF (60 mL). The mixture was stirred for 30 min at 25 °C and recooled to 0 °C. The solution of *N,N*-dimethylthiocarbamic acid chloride (12.4 g, 1.25 equiv) in DMF (20 mL) was added, and the mixture was warmed to 80 °C for 2 h. It was recooled to 20 °C, Et_2O (500 mL) was added, and the organic solution was washed with water (2 × 250 mL) and with aqueous $KHCO_3$ solution. It was dried, and the solvent was evaporated in vacuo. The residue was recrystallized from CH_3OH to give a solid (32.3 g, 89% yield, mp 178–179 °C).

***S*-[4,6-Dichloro-2-[bis(4-fluorophenyl)methyl]phenyl] *N,N*-dimethylthiocarbamate (70).** Ester **69** (32 g) was heated to 275 °C under N_2 for 30 min. The cold mixture was dissolved in the minimum amount of hot *n*-hexane. Charcoal (2 g) was added. The mixture was refluxed for 10 min and filtered hot. From the filtrate crystallized a solid (25.5 g, 80% yield, mp 130–131 °C).

4,6-Dichloro-2-[bis(4-fluorophenyl)methyl]thiophenol (8pp). A solution of **70** (6.2 g) in Et_2O was added dropwise at 0 °C to the suspension of $LiAlH_4$ (0.8 g) in Et_2O (50 mL). The mixture was stirred for 90 min at 25 °C. At 0 °C, 2 N H_2SO_4 was added dropwise to pH 3. The aqueous phase was extracted with Et_2O. The combined organic phases were dried, and the solvent was evaporated in vacuo. Solvent traces were removed in vacuo to leave a thick oil (5.2 g, 100% yield) that was pure according to TLC and ^1H NMR. Anal. ($C_{19}H_{12}Cl_2F_2S$) C, H, Cl.

4(*R*)-Hydroxy-6(*S*)-[[2,4-dichloro-6-(cyclohexyldifluoromethyl)phenoxy]methyl]tetrahydropyran-2-one (4qq). Monofluorolactone 4y (183 mg) was given at 0 °C to anhydrous HF (1 mL), contained in a polyethylene vessel. The mixture was stirred for 5 h under argon at 0 °C. The mixture was diluted with CH_2Cl_2 (20 mL), poured on solid NaF (5 g), and stirred overnight at ambient temperature. It was filtered, and the solid was washed with CH_2Cl_2. The filtrate was evaporated in vacuo. The residue was chromatographed through silica with CH_2Cl_2/EtOAc 4:1 to give a colorless glass (75 mg, 40% yield) that was pure by TLC and ^1H, ^{13}C, and ^{19}F NMR (see Table X of the supplementary material).

4(*R*)-(*tert*-Butyldiphenylsiloxy)-6(*S*)-[[2,4-dimethyl-6-(cyclohexylchloromethyl)phenoxy]methyl]tetrahydropyran-2-one (25rr). A solution of α,α-dimethylbutanoyl chloride (245 mg, 1.8 mmol, 3 equiv) in CH_2Cl_2 (3 mL) was added at 5 °C to a solution of alcohol **25q** (370 mg, 0.6 mmol, 1 equiv) and DMAP (230 mg, 1.9 mmol, 3 equiv) in CH_2Cl_2 (8 mL) and pyridine (230 mg, 2.9 mmol, 5 equiv). The mixture was stirred for 1 h at 25 °C, then diluted with CH_2Cl_2 (50 mL), washed with ice/water, and dried (Na_2SO_4). The drying agent was washed with toluene (25 mL) containing 1% pyridine. The filtrate was evaporated in vacuo. The residue was chromatographed through silica that had been prewashed with toluene (150 mL), containing 1% pyridine, then with toluene (200 mL). Toluene/EtOAc 98:2 was used as the solvent. A glass (310 mg, 74% yield) was obtained.

Biological Assays. The HMG-CoA reductase inhibition assay (Table II), the assay for inhibition of acetate incorporation into cholesterol in cultures of HEP G2 cells (Table III), and the determination of hypocholesterolemic activity in vivo after po administration of test compounds to NZW-rabbits (Table V) were conducted as described before.[1]

The inhibition of hepatic cholesterol de novo synthesis in vivo after po administration of test compounds to rats (Table IV) was determined as described in ref 58d.

Hypocholesterolemic Activity in Male Beagle Dogs (Table VI). The dosage of test compound indicated in Table VI (neat) was administered in gelatine capsules (size 000) daily in the afternoon (3:00 p.m.) for the period indicated to four male beagle dogs. A control group, consisting of four male beagle dogs of comparable body weight, obtained empty gelatine capsules. At the end of the treatment period, venous blood was collected (after fasting overnight) in the morning (8:00 a.m.) from the individual animals. The serum lipoproteins of the individual blood samples were separated with a preparative ultracentrifuge (density criteria: 1.006/1.063/1.21). Safety parameters SGOT, SGPT, aP, bilirubine, and creatinine indicated no appreciable pathologic event. The difference of the average of the plasma LDL levels of the treated animals to that of the control group is listed in Table VI.

Effect on Serum Lipoproteins and Other Metabolic Parameters after Subchronic Oral Administration to Male Rats (Table VII). Test compounds dissolved in polyethylene glycol 400 were administered in the morning in the daily dosage indicated in Table VII via gavage to groups (n = 10) of male rats of the strain HOE:WISKf (SPF 71) with initial body weights exceeding 180 g. Only vehicle was administered to the control group. The animals obtained food and water ad libitum. After the last (seventh) administration, animals were fasted. Blood samples were collected 24 h later from each individual animal retroorbitally under a mild ether narcosis. Immediately thereafter, the animals were sacrificed by spinal distorsion. The liver weight, body weight, and total food consumption were determined. Serum total cholesterol content was determined enzymatically from the blood of each individual animal by test combination of Boehringer-Mannheim (CHOD-PAP high-performance method). For determination of serum lipoproteins, the serum of all rats of one group was pooled, and serum lipoproteins were separated with a preparative ultracentrifuge. The following conditions were used for separation of the fractions VLDL, LDL, and HDL:

		density
1	VLDL	<1.006
2	LDL	1.006–1.04
3	HDL	1.04–1.21

The determination of the protein was according to the method of Lowry et al.[69] From the pooled serum of a group, total glycerol was determined (GPO-PAP high-performance method, Boehringer-Mannheim).

Inhibition of Microsomal Lipid Peroxidation (Table VIII, Left Side). Lipid peroxidation was assayed in rat liver microsomal fractions by measuring thiobarbituric acid reactive substances. Microsomal fractions were diluted with 50 mM TRIS-HCl, pH 7.4, containing KCl (100 mM) and $MgCl_2$ (6.0 mM). Final protein concentration in the incubation mixture amounted to 0.4 mg/mL. Lipid peroxidation was initiated with ADP (2 mM)/$FeCl_3$ (10 μM) and a NADPH-regenerating system.[70] Samples were incubated at 37 °C for 30 min in a shaking water bath. Thiobarbituric acid reactive material was determined and the absorbance was measured at 535 nm.[71]

Inhibition of Cu^{2+}-Catalyzed LDL Oxidation (Table VIII, Right Side). LDL was isolated from porcine plasma containing EDTA (1 mg/mL) by sequential ultracentrifugation in salt solutions of NaCl/NaBr between densities of 1.019 and 1.063 g/mL.[72] LDL was then dialyzed against phosphate-buffered saline (160 mM NaCl, 10 mM NaH_2PO_4), pH 7.4, and stored under N_2 at 4 °C. Prior to the oxidation process, LDL fractions were diluted with phosphate-buffered saline to the final protein concentration of 0.1 mg/mL, and 2.5-mL aliquots were preincubated with test compounds (25 μL of ethanolic solution) for 1 h at 37 °C capped under N_2.[73] For Cu^{2+}-catalyzed oxidation of LDL, 12.5 μL of 1 mM $CuSO_4$ was added to each sample to attain a concentration of 5 μM Cu^{2+}. Incubation was carried out at 37 °C for 2 h under an air atmosphere, and fluorescence intensity was measured at 430 nm with excitation at 365 nm.[74]

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Supplementary Material Available: Spectral data of β-hydroxy lactones 4, *tert*-butyl esters 10, and corresponding β,δ-dihydroxy sodium carboxylates 11 are collected in Table X, and physical and spectral data and yield of phenolic building blocks 8 are collected in Table XI (11 pages). Ordering information is given on any current masthead page.

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