mol) of 6 and 10 mL of HCOOH was heated at reflux for 14 h. Then, 200 mL of water was added and the solution was made basic (pH 9) by addition of sodium carbonate. The resulting solution was extracted with benzene (2 × 150 mL); the organic extracts were dried ($Na_2SO_4$) and evaporated to give a residue, which crystallized as yellow needles from acetone–hexane. 11: $^1H$ NMR (DMSO) 9.22 (1 H, s, C1-H), 8.97 (1 H, ex, t, $NHCH_2$), 8.40 (2 H, t, C10-H and C7-H), 8.00 (1 H, d, $J$ = 8.6, C3-H), 7.92 (1 H, t, C9-H), 7.59 (1 H, t, C8-H), 6.83 (1 H, d, $J$ = 9.0, C4-H), 3.46 (2 H, qu*, $-NHCH_2CH_2-$), 2.62 (2 H, t, $CH_2CH_2NMe_2$), 2.28 (6 H, s, $N(CH_3)_2$).

Compounds 12, 13, and 16–22 were obtained in an analogous manner. Compound 14 required a refluxing time of 28 h.

(b) **5-[[2-(Dimethylamino)ethyl]amino]-1-octylimidazo-[4,5,1-*de*]acridin-6-one (15).** A mixture of 1.48 g (0.004 mol) of hydrochloride 6, 8 mL (0.045 mol) of nonanoic acid, and 10 mL of bromobenzene was heated at reflux for 12 h. After cooling, the solution was diluted with $CHCl_3$ (100 mL) and extracted with 5% aqueous HCl. The aqueous extracts were made basic with NaOH and extracted with benzene. The organic extracts, dried with $CaCl_2$, were evaporated to dryness, and the crude product was crystallized from benzene–heptane. 15: $^1H$ NMR ($CD_3OD$) 8.56 (1 H, d, C7-H), 8.20 (1 H, d, C10-H), 7.92 (1 H, t, C9-H), 7.88 (1 H, d, $J$ = 8.8, C3-H), 7.59 (1 H, t, C8-H), 6.84 (1 H, d, $J$ = 8.9, C4-H), 3.66–0.88 (27 H, m, series of overlapping signals relative to the aliphatic moieties).

**Acknowledgment.** This work was supported by Polish Project CPBR 11.5 and by Italian Ministero della Pubblica Instruzione (Fondi 60%). We thank E. Augustin for the determination of cytotoxic activity against $HeLaS_3$ cells in tissue culture, K. Maturska for skillful technical assistance in animal experiments, and F. Lupidi for NMR spectra.

**Registry No.** 3, 99139-99-8; 3·HCl, 123381-64-6; 3·$MeSO_3H$, 99140-00-8; 4, 99140-23-5; 4·HCl, 123381-65-7; 4·$MeSO_3H$, 99140-24-6; 5, 123381-83-9; 5·HCl, 123381-66-8; 6, 123381-84-0; 6·2HCl, 123381-67-9; 7, 123381-85-1; 7·2HCl, 123381-68-0; 8, 123381-86-2; 8·2HCl, 123381-69-1; 9, 123381-87-3; 9·2HCl, 123381-70-4; 10, 123381-88-4; 10·2HCl, 123381-71-5; 11, 123381-89-5; 11·2HCl, 123381-72-6; 12, 123381-90-8; 12·2HCl, 123381-73-7; 13, 123381-91-9; 13·2HCl, 123381-74-8; 14, 123381-92-0; 14·2HCl, 123381-75-9; 15, 123381-93-1; 15·2HCl, 123381-76-0; 16, 123381-94-2; 16·2HCl, 123381-77-1; 17, 123381-95-3; 17·2HCl, 123381-78-2; 18, 123381-96-4; 18·2HCl, 123411-29-0; 19, 123381-97-5; 19·2HCl, 123381-79-3; 20, 123381-98-6; 20·2HCl, 123381-80-6; 21, 123381-99-7; 21·2HCl, 123381-81-7; 22, 123382-00-3; 22·2HCl, 123381-82-8; $Me_2N(CH_2)_2NH_2$, 108-00-9; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_5NH_2$, 3209-46-9; $EtCO_2H$, 79-09-4; $PrCO_2H$, 107-92-6; $Me_2CHCO_2H$, 79-31-2; $PhCO_2H$, 65-85-0; 1-chloro-4-nitroacridin-9(10*H*)-one, 20621-51-6; nonanoic acid, 112-05-0.

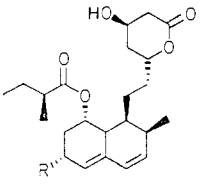
# Synthesis and Biological Activity of New HMG-CoA Reductase Inhibitors. 1. Lactones of Pyridine- and Pyrimidine-Substituted 3,5-Dihydroxy-6-heptenoic (-heptanoic) Acids

G. Beck, K. Kesseler, E. Baader, W. Bartmann,* A. Bergmann, E. Granzer, H. Jendralla, B. v. Kerekjarto, R. Krause, E. Paulus, W. Schubert, and G. Wess

*Hoechst AG, Postfach 80 03 20, 6230 Frankfurt/M. 80, West Germany.* *Received October 24, 1988*

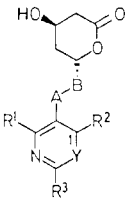
Lactones of pyridine- and pyrimidine-substituted 3,5-dihydroxy-6-heptenoic (-heptanoic) acids **2–4** have been synthesized. Extensive exploration of structure-activity relationships led to several compounds exceeding the inhibitory activity of mevinolin (1b) on HMG-CoA reductase, both in vitro and in vivo. First clinical trials with **2i** (HR 780) are in preparation.

Only a few years after the discovery of the LDL receptor by Brown and Goldstein in 1973,[1] the fungal metabolites compactin (**1a**)[2,3] and mevinolin (**1b**)[4,5] have been isolated. Both compounds are potent inhibitors of cholesterol biosynthesis at the level of the major rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase). Through a feedback mechanism, inhibition of HMG-CoA reductase results in an increase of LDL-receptor synthesis with subsequent removal of LDL from the bloodstream.[6]



1a: R = H

1b: R = $CH_3$



2: A–B = (E)-CH=CH; Y = CH, N

3: A–B = (Z)-CH=CH; Y = CH, N

4: A–B = $CH_2$-$CH_2$ ; Y = CH, N

(1) Goldstein, J. L.; Brown, M. S. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2804.

(2) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiotics* **1976**, *29*, 1346. (b) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1165.

(3) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffmann, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirshfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 3957.

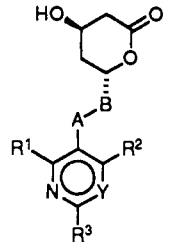
(4) (a) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849. (b) Mol, M. J. T. M.; Erkelens, D. W.; Gevers Leuven, J. A.; Schouten, J. A. *Lancet* **1986**, 936.

(5) (a) Serizawa, N.; Nakagawa, K.; Hamano, K.; Tsujita, Y.; Terahara, A.; Kuwano, H. *J. Antibiotics* **1983**, *36*, 5. (b) *Drugs Future* **1987**, *12*, 437.

(6) Brown, M. S.; Goldstein, J. L. *Sci. Am.* **1984**, 52.

0022-2623/90/1833-0052$02.50/0 

Table I. Physical Properties and Inhibitory Activities of Lactones 2–4



2: A–B = (*E*)-CH=CH
3: A–B = (*Z*)-CH=CH
4: A–B = $CH_2CH_2$

| no. | Y | $R^1$ | $R^2$ | $R^3$ | purifcn[a] | % yield[b] | formula | mp, °C | anal.[c] | $IC_{50}$,[d] nM |
|---|---|---|---|---|---|---|---|---|---|---|
| **1b** | – | – | – | – | – | – | – | – | – | 8 |
| **2a** | CH | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | A | 16 | $C_{20}H_{20}FNO_3$ | 205 | C, H, F, N | 260 |
| **2b** | CH | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | A | 15 | $C_{20}H_{20}ClNO_3$ | oil | C, H, Cl, N | 94 |
| **2c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | B | 13 | $C_{25}H_{22}FNO_3$ | 149 | C, H, F, N | 38 |
| **2d** | CH | $C_2H_5$ | 4-$FC_6H_4$ | $C_6H_5$ | C | 13 | $C_{26}H_{24}FNO_3$ | oil | C, H, F, N | 40 |
| **2e** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $CH_3$ | C | 23 | $C_{22}H_{24}FNO_3$ | oil | C, H, F, N | 9 |
| **2f** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | C | 28 | $C_{24}H_{28}FNO_3$ | 137–140 | C, H, F, N | 3 |
| **2g** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *t*-$C_4H_9$ | C | 16 | $C_{25}H_{30}FNO_3$ | 158–160[e] | C, H, F, N | 1 |
| **2h** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | C | 13 | $C_{27}H_{32}FNO_3$ | 135–138 | C, H, F, N | 4 |
| **2i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | C | 24 | $C_{27}H_{26}FNO_3$ | 141[f,g] | C, H, F, N | 3 |
| **2j** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | C | 22 | $C_{27}H_{25}F_2NO_3$ | oil | C, H, F, N | 2 |
| **2k** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 2,5-$(CH_3)_2C_6H_3$ | C | 28 | $C_{29}H_{30}FNO_3$ | oil | C, H, F, N | 5 |
| **2l** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 3,5-$(CH_3)_2C_6H_3$ | C | 26 | $C_{29}H_{30}FNO_3$ | 80 | C, H, F, N | 8 |
| **2m** | CH | *i*-$C_3H_7$ | 4-$CH_3OC_6H_4$ | $C_6H_5$ | C | 30 | $C_{28}H_{29}NO_4$ | oil | C, H, N | 13 |
| **2n** | CH | *i*-$C_3H_7$ | 4-$CF_3C_6H_4$ | $C_6H_5$ | C | 21 | $C_{28}H_{26}F_3NO_3$ | oil | C, H, F, N | 36 |
| **2o** | CH | *t*-$C_4H_9$ | 4-$FC_6H_4$ | $C_6H_5$ | C | 19 | $C_{28}H_{28}FNO_3$ | oil | C, H, F, N | 18 |
| **2p** | CH | *c*-$C_6H_{11}$ | 4-$FC_6H_4$ | $C_6H_5$ | C | 11 | $C_{30}H_{30}FNO_3$ | 196–198 | C, H, F, N | 30 |
| **2q** | CH | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_6H_5$ | C | 25 | $C_{27}H_{26}FNO_3$ | oil | C, H, F, N | 4 |
| **2r** | N | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | D | 18 | $C_{19}H_{19}FN_2O_3$ | 174–176[h] | C, H, F, N | 500 |
| **2s** | N | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | D | 20 | $C_{19}H_{19}ClN_2O_3$ | oil | C, H, Cl, N | 600 |
| **2t** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | E | 13 | $C_{23}H_{27}FN_2O_3$ | oil | C, H, F, N | 3 |
| **2u** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | C | 19 | $C_{26}H_{31}FN_2O_3$ | 128 | C, H, F, N | 1 |
| **2v** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | D | 18 | $C_{26}H_{25}FN_2O_3$ | 164–166[i] | C, H, F, N | 3 |
| **2w** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | C | 22 | $C_{26}H_{24}F_2N_2O_3$ | 138–140 | C, H, F, N | 1 |
| **3a** | CH | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | A | 8 | $C_{20}H_{20}FNO_3$ | 188 | C, H, F, N | >1000 |
| **3c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | B | 8 | $C_{25}H_{22}FNO_3$ | 216 | C, H, F, N | 100 |
| **3s** | N | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | D | 18 | $C_{19}H_{19}ClN_2O_3$ | 165–166 | C, H, Cl, N | >1000 |
| **4d** | CH | $C_2H_5$ | 4-$FC_6H_4$ | $C_6H_5$ | – | 17 | $C_{26}H_{26}FNO_3$ | 53–55 | C, H, F, N | 3 |
| **4i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | – | 22 | $C_{27}H_{28}FNO_3$ | oil | C, H, F, N | 19 |
| **4r** | N | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | – | 18 | $C_{19}H_{21}FN_2O_3$ | 170–172 | C, H, F, N | 1000 |

[a] Purified by flash chromatography on silica using the following eluents: A ethyl acetate/methanol 10:1, B cyclohexane/ethyl acetate 1:4, C cyclohexane/ethyl acetate 2:1, D ethyl acetate, E cyclohexane/ethyl acetate 1:1. [b] Represents overall yield for purified material from Wittig reaction of 6. [c] Analytical results for purified material were within ±0.4% of the theoretical values. [d] Tested in the ring-opened potassium dihydroxycarboxylate form, for assay protocol see the Experimental Section. [e] $[\alpha]^{20}_D = +26°$ (*c* = 1, methanol). [f] $[\alpha]^{20}_D = +25°$ (*c* = 1, methanol). [g] Obtained as an oil, which crystallized on standing for several weeks; melting point determined after recrystallization from diisopropyl ether/ethyl acetate 2:1. [h] $[\alpha]^{20}_D = +21°$ (*c* = 1, methanol). [i] $[\alpha]^{20}_D = +14°$ (*c* = 1, methanol).

Recent reports by Merck Sharp & Dohme,[7] Sandoz,[8] and Warner-Lambert[9] have described natural products and synthetic analogues related to mevinolin (**1b**). In our laboratories structurally simplified HMG-CoA reductase inhibitors have been synthesized as well.[10,11] Structure–activity relationships (SAR) in previous series[7,10,11] revealed that the chiral lactone moiety in mevinolin (**1b**) is essential for strong biological activity, whereas the hexahydronaphthalene moiety allows more structural variations. In the present paper we describe the synthesis and biological activity of new HMG-CoA reductase inhibitors **2–4**, which contain for the first time monocyclic,[12] six-membered

(7) (a) Stokker, G. E.; Hoffmann, 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) Hoffmann, 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. F.; Hoffmann, 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. (d) Hoffmann, W. F.; Alberts, A. W.; Anderson, P. S.; Chen, J. S.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1986**, *29*, 849. (e) Stokker, G. E.; Alberts, A. W.; Gilfillan, J. L.; Huff, J. W.; Smith, R. L. *J. Med. Chem.* **1986**, *29*, 852.

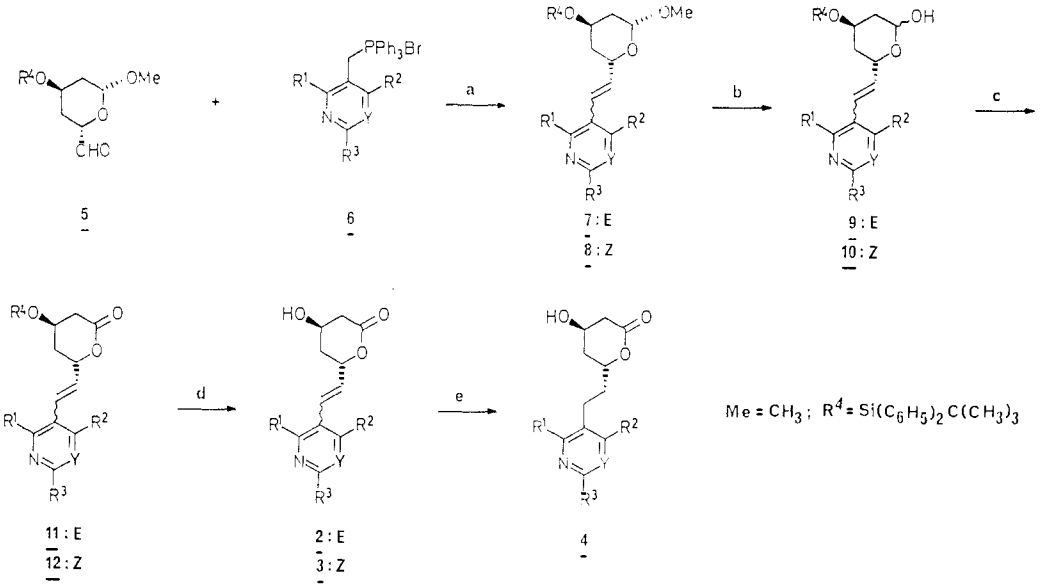
(8) (a) Sandoz, patent WO 84/02131, 1984. (b) Sandoz, patent WO 86/00307, 1986. (c) Sandoz, patent WO 86/07054, 1986. (d) Sandoz, European Application EP-A-0221025, 1987.

(9) Warner-Lambert, European Application EP-A-0179559, 1986.

(10) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Kesseler, K.; Krause, R.; Paulus, E. F.; Schubert, W.; Wess, G.; 4th. International Conference of Chemistry and Biotechnology of Biologically Active Natural Products, Budapest, August 10–14, 1987, submitted for publication (Raven Press, New York).

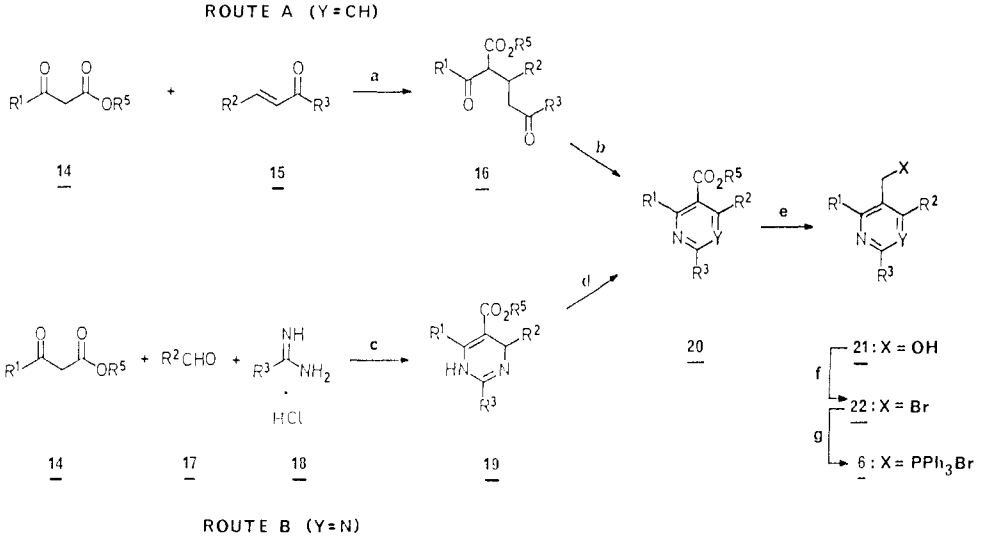
(11) (a) Bartmann, W.; Beck, G.; Granzer, E.; Jendralla, H.; v. Kerekjarto, B.; Wess, G. *Tetrahedron Lett.* **1986**, *27*, 4709. (b) Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G.; Schubert, W.; Granzer, E.; v. Kerekjarto, B.; Krause, R. *Tetrahedron Lett.* **1988**, *29*, 929.

**Scheme I**[a]




[a] (a) *n*-BuLi, THF, 0–20 °C, (b) HOAc, $H_2O$, THF, reflux, (c) NIS, TBAI, $CH_2Cl_2$, 20 °C, (d) TBAF, HOAc, THF, 20 °C, (e) $H_2$, Pd/C cat., MeOH, EtOAc, 20 °C.

**Scheme II**[a]




[a] (a) KO-*t*-Bu cat., *i*-$Pr_2O$, 20 °C, (b) $NH_4OAc$, $FeCl_3 \cdot 6H_2O$, HOAc, reflux, (c) KOAc, PhMe, reflux, (d) DDQ, PhMe, reflux, (e) $LiAlH_4$, THF, 20 °C, (f) $PBr_3$, $CH_2Cl_2$, 20 °C, (g) $PPh_3$, PhMe, reflux.

heteroaromatic groups with basic properties.

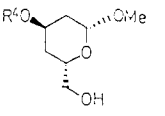
## Chemistry

The new compounds **2–4** were synthesized in optically pure form by the general method shown in Scheme I and are listed in Table I. Compounds **2** were obtained through Wittig reaction with the chiral aldehyde **5** and ylides generated from the phosphonium salts **6**, followed by cleavage of the lactol ether moiety of **7**, oxidation of **9** to lactones **11**, and desilylation. *Z*-configurated analogues **3** were prepared through the general sequence **8** → **10** → **12** → **3**.

The Wittig reaction proceeded with high stereoselectivity, leading predominantly to the biologically more potent *E* isomers. Double-bond geometry was assigned on the basis of the $^1H$ NMR coupling constants of the olefinic protons (*E* isomers, $J$ = 16 Hz; *Z* isomers, $J$ = 11 Hz).

The saturated analogues **4** were synthesized by catalytic hydrogenation of compounds **2** or **3**.

In all cases, the configuration of the lactone moiety results from synthesis via the optically pure 4*R*,6*S* aldehyde **5**.[13] Compound **5** was easily prepared through Swern oxidation[14] of the corresponding alcohol **13**,[13] obtained stereoselectively from glucose.



**13**

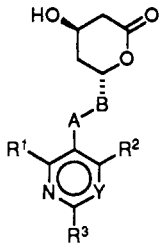
For compound **2i** the assigned relative configuration has been additionally confirmed by X-ray crystallographic analysis.

(12) Quinoline-containing HMG-CoA reductase inhibitors have recently been produced by Warner-Lambert, U.S. Patent 4761419 A, 1988.

(13) Yang, Y. L.; Falck, J. R. *Tetrahedron Lett.* **1982**, *23*, 4305.

(14) Swern, D.; Manusco, A.; Huany, S. *J. Org. Chem.* **1978**, *43*, 2480.

Table II. Inhibitory Effect of Compounds 2–4 on the de Novo Cholesterol Biosynthesis of HEP-G2 Cell Cultures[a]



2: A–B = (*E*)-CH=CH
3: A–B = (*Z*)-CH=CH
4: A–B = $CH_2CH_2$

| no. | Y | $R^1$ | $R^2$ | $R^3$ | $IC_{50}$, nM | rel potency[b] |
|---|---|---|---|---|---|---|
| **1b** | – | – | – | – | 50 | 1.00 |
| **2a** | CH | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | 2000 | 0.03 |
| **2c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | 90 | 0.56 |
| **2e** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $CH_3$ | 50 | 1.00 |
| **2g** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *t*-$C_4H_9$ | 20 | 2.50 |
| **2h** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | 9.5 | 5.26 |
| **2i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | 5.0 | 10.00 |
| **2j** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | 7.5 | 6.67 |
| **2k** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 2,5-$(CH_3)_2$-$C_6H_3$ | 20 | 2.50 |
| **2m** | CH | *i*-$C_3H_7$ | 4-$CH_3OC_6H_4$ | $C_6H_5$ | 150 | 0.33 |
| **2p** | CH | *c*-$C_6H_{11}$ | 4-$FC_6H_4$ | $C_6H_5$ | >5000 | >0.01 |
| **2q** | CH | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_6H_5$ | 10 | 5.00 |
| **2t** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | 4.8 | 10.42 |
| **2u** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | 26 | 1.92 |
| **2y** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | 5 | 10.00 |
| **2w** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | 18 | 2.78 |
| **3c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | 5000 | 0.08 |
| **4i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | 370 | 0.14 |

[a] For assay protocol, see the Experimental Section. [b] Potency of mevinolin (**1b**) was arbitrarily assigned a value of 1.00.

The synthesis of phosphonium salts **6**, via esters **20**, is outlined in Scheme II. Pyridine esters **20** (Y = CH) were obtained through Michael addition[15] of keto esters **14**[16] and enones **15**,[17] followed by oxidative cyclization[18] of the intermediate 1,5-diketones **16** (route A, see Table III). Pyrimidine esters **20** (Y = N) were synthesized through condensation of **14** with aldehydes **17** and amidinium salts **18**,[19] followed by oxidation of the resulting 1,4-dihydropyrimidines **19** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; route B, see Table III). In all cases, esters **20** were transformed to phosphonium salts **6** in three steps via reduction, halogenation of the resulting alcohols **21**, and finally reaction of bromides **22** with triphenyl phosphine (see Table IV).

## Biological Results and Discussion

The new pyridine and pyrimidine analogues **2–4** (Table I) were evaluated for their ability to inhibit solubilized, partially purified rat liver HMG-CoA reductase in vitro. Compounds **2–4** were also investigated for inhibition of cellular HMG-CoA reductase in cultures of hepatic cells (HEP G2, a human hepatoma cell line), determined by decreased incorporation of sodium [$^{14}$C]acetate into cholesterol (Table II). Selected compounds were further evaluated for their ability to inhibit hepatic cholesterol synthesis and to decrease cholesterol levels in several animal species upon po administration.[20]

All biological experiments were performed with optically pure **1b** as reference for direct comparison.

In general, the structure–activity relationships of pyrimidines (**2r–w**) are comparable to those of the corresponding pyridines (**2a–q**) (e.g. **2i** vs **2v**, **2a** vs **2r**, **2j** vs **2w**; Table I). The inhibitory potency strongly depends on the substitution pattern of the heteroaromatic ring. We[10–12] and others[7] have recently shown that substitution in 2-, 4-, and 6-position of the central aromatic ring leads to strong biological activity.

However, through appropriate choice of substituents, the inhibitory potency of the compounds can be further increased by 3 orders of magnitude.

The biological activity of compounds **2** reaches a maximum if an isopropyl group is introduced in position 2 of the central heteroaromatic ring (e.g. **2i** vs **2o**, **2p**, **2d**, and **2a**). Polar substituents in position 4, which seem to mimic the polar ester moiety of mevinolin, have previously been shown to result in compounds with high activity.[7]

In our series 4-(chlorophenyl)- and 4-(fluorophenyl)-substituted analogues are equally potent inhibitors (e.g. **2a** vs **2b**, **2r** vs **2s**). 4-(Methoxyphenyl) or 4-[(trifluoromethyl)phenyl] substitution leads to significant loss of activity (**2m**, **2n**, vs **2i**).

Substitution in position 6 turns out to be the most critical for optimal biological activity. Marked increase of potency is obtained not only by introduction of bulky alkyl groups (e.g. **2f**, **2g**, **2h**, **2t** vs **2e**, **2s**) but also by the use of phenyl moieties (e.g. **2i**, **2j**, **2k**, **2v**, **2w**).

In order to further understand the structure–activity relationships, inhibitor **2i** was compared with mevinolin (**1b**) by using computer-assisted methods.

For both compounds a conformational analysis was carried out in order to determine their low-energy conformations. Structure **2i** was fitted to **1b** by reorienting it as a whole and allowing groups to move independently (for details, see the Experimental Section).

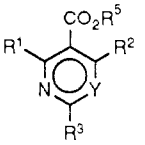
A graphical representation of the fit of **2i** against **1b** is shown in Figure 1. If the lactone moieties are oriented the same way in both conformers, the isopropyl group of **2i** occupies partly the region of the hexahydronaphthalene system of **1b**. At the same time the 4-fluorophenyl group of **2i** occupies most of the space of the ester group of **1b**. The phenyl ring of **2i**, however, completely extends beyond the volume of **1b**.

Since **2i** and all other compounds bearing bulky substituents as $R^3$ (e.g. **2f**, **2h**, **2j**, **2n**, **2t**, **2w**) are more potent than mevinolin, one might speculate that $R^3$ serves as an additional anchor, interacting with a second hydrophobic region of the enzyme and thus increases binding. A final explanation might be expected by the elucidation of the tertiary structure of the HMG-CoA reductase. All *Z* double bond isomers **3** showed only weak in vitro activity (e.g. **3a**, **3c**, **3r**). Also hydrogenation of *E* isomers **2** in most cases significantly decreased inhibitory potency (e.g. **2i** vs **4i**, **2r** vs **4r**). However, rather unexpectedly, **4d** was 10 times more active in vitro than **2d**. This points to a delicate balance[21] between the length of the carbon bridge and the steric bulk of $R^1$ with regard to adaptation of the inhibitor to the active site of the enzyme.

(15) Connor, R.; Andrews, D. B. *J. Am. Chem. Soc.* **1934**, *56*, 2713.
(16) Jackman, M.; Klenk, M.; Fishburn, B.; Tullar, B. F.; Archer, S. *J. Am. Chem. Soc.* **1948**, *70*, 2884.
(17) (a) Drake, N. L.; Allen, P. In *Organic Synthesis*; John Wiley & Sons, Inc. New York, 1932; Collect. Vol. I, p 77. (b) Kohler, E. L.; Chadwell, H. M. *Ibid.* p 78.
(18) Rehberg, R.; Kroehnke, F. *Justus Liebigs Ann. Chem.* **1968**, *717*, 91.
(19) (a) Dox, A. W. In *Organic Synthesis*; Wiley and Sons Inc., New York, **1932**; Collect. Vol. I, p 5. (b) Brown, D. J.; Lan, S.; Mori, K. *Aust. J. Chem.* **1984**, *37*, 2093. (c) Hagemeyer, J. H.; Gammans, W. J. U.S. 3, 402, 193 (Eastman Kodak Co.); *Chem. Abstr.* **1960**, *70*, 3316.

(20) Results will be published separately.

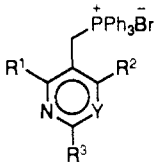
Table III. Physical Properties of Esters 20



| no. | Y | $R^1$ | $R^2$ | $R^3$ | $R^5$ | purifica | % yield[b] | formula | mp, °C | anal.[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| **20a** | CH | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | $CH_3$ | A | 66 | $C_{15}H_{14}FNO_2$ | oil | C, H, F, N |
| **20b** | CH | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | $CH_3$ | B | 73 | $C_{15}H_{14}ClNO_2$ | oil | C, H, Cl, N |
| **20c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | B | 69 | $C_{21}H_{18}FNO_2$ | oil | C, H, F, N |
| **20d** | CH | $C_2H_5$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | C | 28 | $C_{22}H_{20}FNO_2$ | oil | C, H, F, N |
| **20e** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $CH_3$ | $C_2H_5$ | D | 58 | $C_{18}H_{20}FNO_2$ | oil | C, H, F, N |
| **20f** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_2H_5$ | C | 68 | $C_{20}H_{24}FNO_2$ | oil | C, H, F, N |
| **20g** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *t*-$C_4H_9$ | $C_2H_5$ | E | 46 | $C_{21}H_{26}FNO_2$ | oil | C, H, F, N |
| **20h** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | $C_2H_5$ | E | 45 | $C_{23}H_{28}FNO_2$ | oil | C, H, F, N |
| **20i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | D | 66 | $C_{23}H_{22}FNO_2$ | oil | C, H, F, N |
| **20j** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | $C_2H_5$ | E | 55 | $C_{23}H_{21}F_2NO_2$ | 109–111 | C, H, F, N |
| **20k** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 2,5-$(CH_3)_2C_6H_3$ | $C_2H_5$ | E | 79 | $C_{25}H_{26}FNO_2$ | oil | C, H, F, N |
| **20l** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 3,5-$(CH_3)_2C_6H_3$ | $C_2H_5$ | E | 61 | $C_{25}H_{26}FNO_2$ | oil | C, H, F, N |
| **20m** | CH | *i*-$C_3H_7$ | 4-$CH_3OC_6H_4$ | $C_6H_5$ | $C_2H_5$ | E | 66 | $C_{24}H_{25}NO_3$ | 70–74 | C, H, N |
| **20n** | CH | *i*-$C_3H_7$ | 4-$CF_3C_6H_4$ | $C_6H_5$ | $C_2H_5$ | E | 71 | $C_{24}H_{22}F_3NO_2$ | oil | C, H, F, N |
| **20o** | CH | *t*-$C_4H_9$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | C | 22 | $C_{24}H_{24}FNO_2$ | oil | C, H, F, N |
| **20p** | CH | *c*-$C_6H_{11}$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | C | 55 | $C_{26}H_{26}FNO_2$ | oil | C, H, F, N |
| **20q** | CH | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_6H_5$ | $CH_3$ | D | 52 | $C_{22}H_{20}FNO_2$ | 114 | C, H, F, N |
| **20r** | N | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | $C_2H_5$ | F | 43 | $C_{15}H_{15}FN_2O_2$ | oil | C, H, F, N |
| **20s** | N | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | $C_2H_5$ | F | 47 | $C_{15}H_{15}ClN_2O_2$ | oil | C, H, Cl, N |
| **20t** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_2H_5$ | A | 33 | $C_{19}H_{23}FN_2O_2$ | 141 | C, H, F, N |
| **20u** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | $C_2H_5$ | B | 47 | $C_{22}H_{27}FN_2O_2$ | oil | C, H, F, N |
| **20v** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | $C_2H_5$ | C | 51 | $C_{22}H_{21}FN_2O_2$ | 105 | C, H, F, N |
| **20w** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | $C_2H_5$ | C | 73 | $C_{22}H_{20}F_2N_2O_2$ | 105–108 | C, H, F, N |

[a] Purified by flash chromatography on silica using the following eluents: A cyclohexane/ethyl acetate 2:1, B cyclohexane/ethyl acetate 1:1, C cyclohexane/ethyl acetate 4:1, D cyclohexane/ethyl acetate 3:1, E cyclohexane/ethyl acetate 8:1, F cyclohexane/methanol 9:1. [b] Represents overall yield from Michael reaction of keto esters 14. [c] Analytical results were within ±0.4% of the theoretical values.

Table IV. Physical Properties of Phosphonium Salts 6



| no. | Y | $R^1$ | $R^2$ | $R^3$ | % yield[a] | formula | mp, °C | anal.[b] |
|---|---|---|---|---|---|---|---|---|
| **6a** | CH | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | 65 | $C_{32}H_{28}BrFNP$ | 218–220 | C, H, Br, F, N, P |
| **6b** | CH | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | 32 | $C_{32}H_{28}BrClNP$ | oil | C, H, Br, Cl, N, P |
| **6c** | CH | $CH_3$ | 4-$FC_6H_4$ | $C_6H_5$ | 64 | $C_{37}H_{30}BrFNP$ | 230–232 | C, H, Br, F, N, P |
| **6d** | CH | $C_2H_5$ | 4-$FC_6H_4$ | $C_6H_5$ | 91 | $C_{38}H_{32}BrFNP$ | 218–220 | C, H, Br, F, N, P |
| **6e** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $CH_3$ | 29 | $C_{34}H_{32}BrFNP$ | 209 | C, H, Br, F, N, P |
| **6f** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | 60 | $C_{36}H_{36}BrFNP$ | 100[c] | C, H, Br, F, N, P |
| **6g** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *t*-$C_4H_9$ | 63 | $C_{37}H_{38}BrFNP$ | 100[c] | C, H, Br, F, N, P |
| **6h** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | 64 | $C_{39}H_{40}BrFNP$ | 223–226 | C, H, Br, F, N, P |
| **6i** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | 34 | $C_{39}H_{34}BrFNP$ | 268–274 | C, H, Br, F, N, P |
| **6j** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | 42 | $C_{39}H_{33}BrF_2NP$ | 235–239 | C, H, Br, F, N, P |
| **6k** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 2,5-$(CH_3)_2C_6H_3$ | 54 | $C_{41}H_{38}BrFNP$ | 250 | C, H, Br, F, N, P |
| **6l** | CH | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 3,5-$(CH_3)_2C_6H_3$ | 58 | $C_{41}H_{38}BrFNP$ | 250 | C, H, Br, F, N, P |
| **6m** | CH | *i*-$C_3H_7$ | 4-$CH_3OC_6H_4$ | $C_6H_5$ | 67 | $C_{40}H_{37}BrNOP$ | 270–275 | C, H, Br, N, P |
| **6n** | CH | *i*-$C_3H_7$ | 4-$CF_3C_6H_4$ | $C_6H_5$ | 82 | $C_{40}H_{34}BrF_3NP$ | 250 | C, H, Br, F, N, P |
| **6o** | CH | *t*-$C_4H_9$ | 4-$FC_6H_4$ | $C_6H_5$ | 55 | $C_{40}H_{36}BrFNP$ | 250 | C, H, Br, F, N, P |
| **6p** | CH | *c*-$C_6H_{11}$ | 4-$FC_6H_4$ | $C_6H_5$ | 70 | $C_{42}H_{38}BrFNP$ | 270[c] | C, H, Br, F, N, P |
| **6q** | CH | 4-$FC_6H_4$ | *i*-$C_3H_7$ | $C_6H_5$ | 41 | $C_{39}H_{34}BrFNP$ | 254 | C, H, Br, F, N, P |
| **6r** | N | $CH_3$ | 4-$FC_6H_4$ | $CH_3$ | 45 | $C_{31}H_{27}BrFN_2P$ | 232–236 | C, H, Br, F, N, P |
| **6s** | N | $CH_3$ | 4-$ClC_6H_4$ | $CH_3$ | 56 | $C_{31}H_{27}BrClN_2P$ | 217–219 | C, H, Br, Cl, N, P |
| **6t** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *i*-$C_3H_7$ | 40 | $C_{35}H_{35}BrFN_2P$ | 166–169 | C, H, Br, F, N, P |
| **6u** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | *c*-$C_6H_{11}$ | 42 | $C_{38}H_{39}BrFN_2P$ | oil | C, H, Br, F, N, P |
| **6v** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | $C_6H_5$ | 69 | $C_{38}H_{33}BrFN_2P$ | 272–274 | C, H, Br, F, N, P |
| **6w** | N | *i*-$C_3H_7$ | 4-$FC_6H_4$ | 4-$FC_6H_4$ | 70 | $C_{38}H_{32}BrF_2N_2P$ | 210–214 | C, H, Br, F, N, P |

[a] Represents overall yield from reduction of esters 20. [b] Analytical results were within ±0.4% of the theoretical values. [c] Decomposition.

In HEP G2 cells, lactones **2–4** show comparable structure–activity relationships (SAR) as indicated above for their sodium salts in the enzyme test (Table II). A series of compounds (e.g. **2g–k**, **2v**, **2w**) are more potent in HEP G2 cells than mevinolin.

Inhibition of hepatic cholesterol "de novo" synthesis in vivo after oral administration to rats for selected compounds **2** also exceeds that of mevinolin.[20] Several compounds (e.g. **2i** and **2t**) were also investigated in normolipemic rabbits. Analogue **2i** (10 mg/kg) after oral ad-

(21) Although these results are somewhat conflicting, they are in line with observations made in a series of HMG-CoA reductase inhibitors containing a central phenyl moiety.[7] Depending on the substitution pattern of the aromatic ring, saturation of the ethylenic bridge in some cases decreased activity,[7c] whereas in other cases it increased activity.[7a,b]

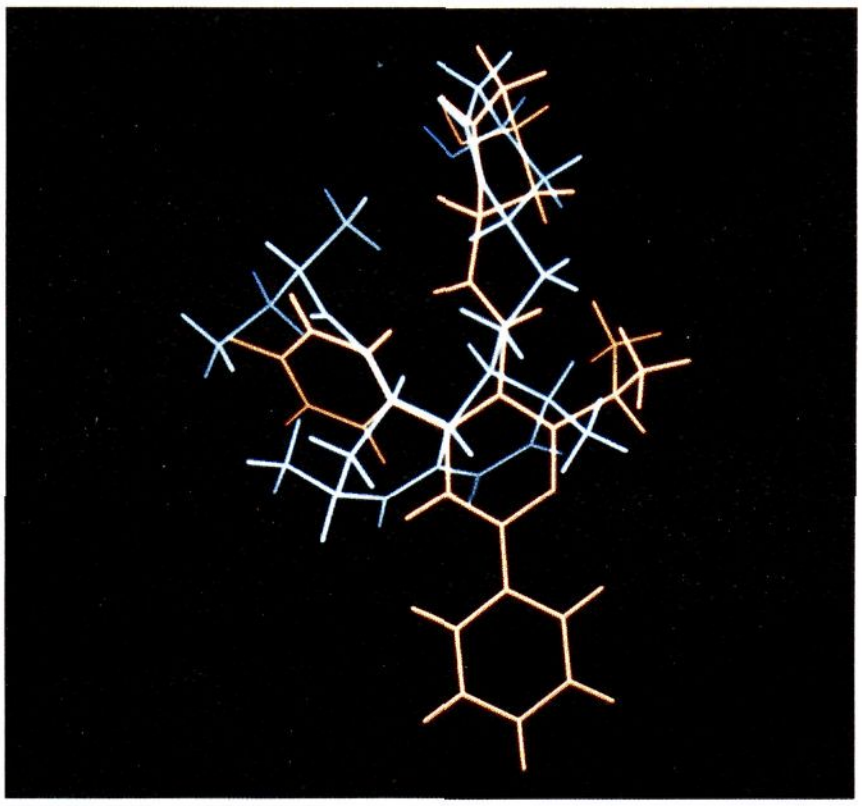


**Figure 1.** Superposition of structures of **1b** (blue) and **2i** (red). Except for the phenyl ring, **2i** occupies the same regions of space as **1b**.

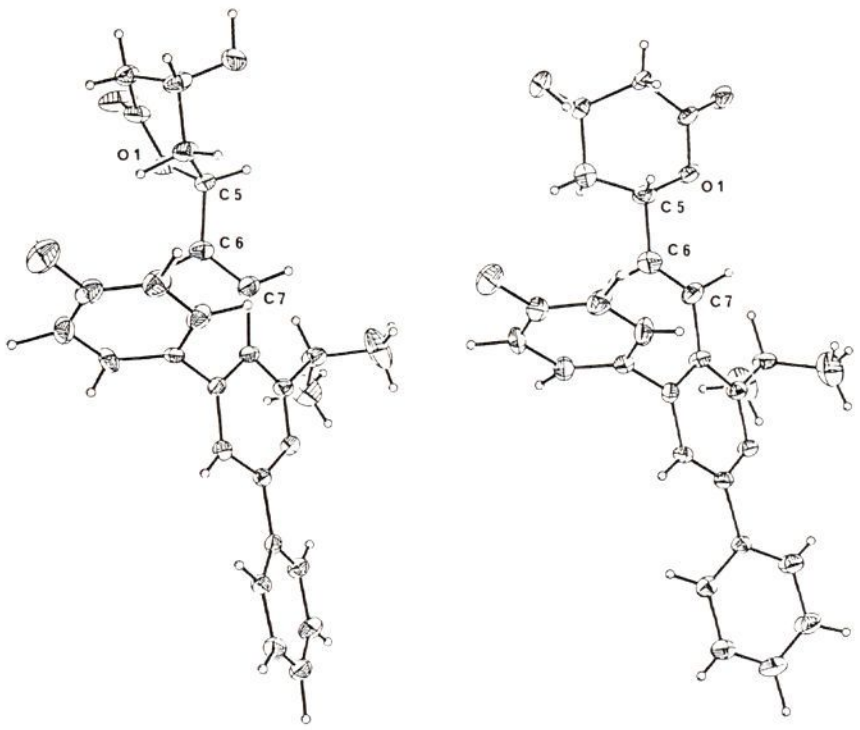



**Figure 2.** Computer-generated ORTEP drawings of conformers A (left) and B (right) of compound **2i** forming an asymmetrical unit within the unit cell.

ministration for 19 days decreased serum total and LDL-cholesterol levels by 35% and 53%, respectively (mevinolin at 10 mg/kg for 19 days: total cholesterol −17%, LDL-cholesterol −30%). Oral treatment with **2t** (5 mg/kg) for 10 days resulted in a 30% decrease of total cholesterol.

## X-ray Crystallography for 2i

The X-ray structure analysis of **2i** resulted in two distinct molecules forming an asymmetric unit, which show quite different conformations (Figure 2). The lactone ring of molecule A adopts a boat conformation; that of molecule B is in the chair conformation. Further, large differences in the torsion angles O1–C5–C6–C7 (43.4° and 130.4°, respectively) were detected. There are no substantial differences in bond lengths or bond angles; all the different planar groups of atoms are not coplanar, because otherwise the steric hindrance would be too large. The dihedral angles between the central pyridine ring and the ethylene bridge, the fluorophenyl, and the phenyl group are 50.8°, 83.2°, and 18.3° (conformer A) and 51.4°, 71.5°, and 17.6° (conformer B). The congruency of the parameters of the two molecules was not optimal, because of the unsatisfactory crystal quality usually obtained when two molecules of different conformation are crystallizing together.

## Conclusion

The pyridine and pyrimidine analogues **2–4** synthesized for this study are potent inhibitors toward HMG-CoA reductase. SAR studies showed that a similar 2,4,6-substitution pattern of the pyridine and pyrimidine ring was necessary for optimal biological activity. Different from SAR studies in other series,[7] we showed that bulky lipophilic substituents in position 6 of the central aromatic ring add significantly to the biological activity of synthetic HMG-CoA reductase inhibitors. A series of compounds **2** and **4** exceeded the activity of mevinolin in HEP G2 cells, as well as in the reduction of plasma cholesterol levels in normolipemic rabbits. Some of these compounds are currently being evaluated for development as antiarteriosclerotic drugs. With the pyridine analogue **2i** (HR 780) toxicological studies in rats and monkeys have already been performed.[20] The first clinical trials with this compound are in preparation.

## Experimental Section

Reaction with materials sensitive to air or moisture were run in dry-glass apparatus under an argon atmosphere with absolute solvents. All reactions were monitored by TLC. Unless noted otherwise, reaction mixtures were worked up by quenching with water, separation of the organic layer, and extraction of the aqueous phase with ether. The combined organic extracts were washed with water or brine, dried over $MgSO_4$, and evaporated on a rotary evaporator. Melting points were determined on a Büchi capillary melting point apparatus (according to Dr. Tottoli) and are uncorrected. $^1H$ NMR spectra were recorded on a Bruker WP60 or WM270 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS 9 (FAB) or MS 80 (CI) mass spectrometer. Optical rotations were determined on a Perkin-Elmer 141 polarimeter.

**β-Keto Esters 14.** These compounds were synthesized according to the method of Jackman.[16]

**Enones 15.** These compounds were prepared according to literature methods.[17]

**Amidinium Hydrochlorides 18.** These compounds were *prepared according to literature,*[19] *if not commercially available.*

**General Procedure for the Synthesis of Pyridine- and Pyrimidine-3-carboxylic Acid Esters 20a–w (Table III). 3-(4-Fluorophenyl)-2-(1-oxoethyl)-5-oxohexanoic Acid Methyl Ester (16a).** A solution of 4-(4-fluorophenyl)but-3-en-2-one (**15a**; 41.0 g, 0.25 mol) in ether (600 mL) was added dropwise to a mixture of methyl acetoacetate (**14a**; 58.1 g, 0.50 mol), potassium hydroxide (1.2 g), and ethanol (12 mL). During the addition, the reaction temperature was kept below 30 °C. The resulting solution was allowed to stand for 3 h, was acidified (pH 5) by addition of acetic acid, and successively shaken with water and saturated $NaHCO_3$ solution. Usual workup gave 50.6 g (72%) of **16a** as a yellow oil, which was used in the next step without purification: $^1H$ NMR δ 0.8–1.0 (6 H, m), 1.9 (3 H, s), 2.2–2.9 (2 H, m), 3.1–4.1 (7 H, m), 7.0–7.8 (4 H, m).

**1,4-Dihydro-4-(4-fluorophenyl)-2-isopropyl-6-phenylpyrimidine-3-carboxylic Acid Ethyl Ester (19v).** To a suspension of benzamidine hydrochloride (**18b**; 102.2 g, 0.85 mol) and potassium acetate (90.7 g, 0.94 mol) in 1.5 L of toluene were added 4-methyl-3-oxopentanoic acid ethyl ester (98.6 g, 0.62 mol) and 4-fluorobenzaldehyde (**17a**; 77.0 g, 0.62 mol); the mixture was stirred for 24 h under reflux, with a Dean–Stark trap, until no more water separated. The reaction mixture was cooled and worked up in the usual manner. The residual oil was chroma-

tographed on silica gel. Elution with cyclohexane/ethyl acetate 4:1 provided **19v** (110 g, 50%) as a viscous, yellow oil: $^1$H NMR $\delta$ 1.2 (3 H, t, $J$ = 7 Hz), 1.3 (6 H, d, $J$ = 7 Hz), 4.0–4.5 (3 H, m), 5.8 (1 H, s), 7.0–7.9 (10 H, m). Anal. ($C_{22}H_{23}FN_2O_2$) C, H, F, N.

**2,6-Dimethyl-4-(4-fluorophenyl)pyridine-3-carboxylic Acid Methyl Ester (20a).** A suspension of **16a** (28.0 g, 100 mmol), ammonium acetate (120 g), and iron(III) chloride hexahydrate (120 g) in acetic acid (1000 mL) was refluxed for 4 h with continuous stirring. The resulting deep red mixture was cooled and filtered. After washing of the remaining solid with toluene and ethanol, the filtrates were combined and evaporated. The residue was suspended in water, neutralized by addition of solid $NaHCO_3$, and worked up as usual. Chromatography gave **20a** (23.6 g, 91%) as a white solid: mp 89–90 °C; $^1$H NMR $\delta$ 2.6 (6 H, s), 3.7 (3 H, s), 7.0–7.5 (5 H, m); MS $C_{15}H_{14}FNO_2$ $m/e$ = 259 ($M^+$). Anal. ($C_{15}H_{14}FNO_2$) C, H, F, N.

**4-(4-Fluorophenyl)-2-isopropyl-6-phenylpyrimidine-3-carboxylic Acid Ethyl Ester (20v).** To a solution of **19v** (24.2 g, 66 mmol) in toluene (300 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 18.0 g, 79 mmol), and the mixture was stirred for 3 h at 50 °C. The reaction mixture was cooled, the solvent was evaporated, and the dark residual oil was extracted five times with cyclohexane/ethyl acetate 4:1 (100 mL). The organic extracts were evaporated and the brown, residual oil was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate 4:1 provided **20v** (19.9 g, 82%): mp 105–107 °C; $^1$H NMR $\delta$ 1.1 (3 H, t, $J$ = 7 Hz), 1.4 (6 H, d, $J$ = 7 Hz), 3.2 (1 H, h, $J$ = 7 Hz), 4.2 (2 H, q, $J$ = 7 Hz), 7.0–8.0 (7 H, m), 8.5–8.8 (2 H, m). Anal. ($C_{22}H_{21}FN_2O_2$) C, H, F, N.

**General Procedure for the Synthesis of Pyridine and Pyrimidine Phosphonium Salts 6a–w (Table IV). [2,6-Dimethyl-4-(4-fluorophenyl)pyridin-3-yl]methanol (21a).** A 1.0 M solution of $LiAlH_4$ in THF (30 mL, 30 mmol) was added to a solution of **20a** (7.80 g, 30.1 mmol) in THF (40 mL). The resulting reaction mixture was stirred at room temperature for 1.5 h and poured onto water. After usual workup, the crystalline residue was washed with a 1:1 mixture of cyclohexane and ethyl acetate, which gave **21a** (6.5 g, 93%) as a white solid: mp 124 °C; $^1$H NMR $\delta$ 2.0 (1 H, s), 2.5 (3 H, s), 2.7 (3 H, s), 4.6 (2 H, s), 6.9 (1 H, s), 7.0–7.5 (4 H, m); MS $C_{14}H_{14}FNO$ $m/e$ = 231 ($M^+$). Anal. ($C_{14}H_{14}FNO$) C, H, F, N.

**Bromo[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]methane (22a).** A solution of **21a** (6.4 g, 27.7 mmol) and phosphorous tribromide (5.3 mL, 54.4 mmol) in a mixture of toluene (50 mL) and dichloromethane (25 mL) was stirred at room temperature for 1 h. The resulting mixture was poured onto saturated $NaHCO_3$ solution and worked up as usual to yield essentially pure **22a** (6.4 g, 79%) as a pale yellow solid, mp 86–87 °C, which was used in the next step without purification: $^1$H NMR $\delta$ 2.5 (3 H, s), 2.7 (3 H, s), 4.4 (2 H, s), 6.9 (1 H, s), 7.0–7.5 (4 H, m); MS $C_{14}H_{13}BrFN$ $m/e$ = 295, 293 ($M^+$). Anal. ($C_{14}H_{13}BrFN$) C, H, F. N.

**[2,6-Dimethyl-4-(4-fluorophenyl)pyridin-3-yl]methyltriphenylphosphonium Bromide (6a).** A solution of **22a** (6.4 g, 22.5 mmol) and triphenylphosphine (6.2 g, 23 mmol) in toluene (200 mL) was refluxed for 5 h. Upon cooling, a white precipitate formed, which was collected on a Büchner funnel, washed with ether, and dried in vacuo to yield analytically pure **6a** (6.4 g, 89%): mp 218–220 °C; $^1$H NMR $\delta$ 2.3 (3 H, d, $J$ = 2 Hz), 2.5 (3 H, d, $J$ = 3 Hz), 6.5 (2 H, d, $J$ = 16 Hz), 6.8–7.9 (20 H, m); MS $C_{32}H_{28}BrFNP$ $m/e$ = 476 ($M^+$). Anal. ($C_{32}H_{28}BrFNP$) C, H, Br, F, N, P.

**General Procedure for the Synthesis of Lactones 2–4 (Table I). (*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]ethenyl]-2(*R*)-methoxy-3,4,5,6-tetrahydro-2*H*-pyrans (7a and 8a).** A 1.6 M solution of $n$-butyllithium in hexane (12 mL, 19.2 mmol) was added dropwise to a solution of **6a** (9.70 g, 17.5 mmol) in THF (100 mL) at 0 °C. The resulting reaction mixture was stirred for 0.5 h, then a solution of **5** (7.29 g, 18.4 mmol) in THF (40 mL) was added, and the stirring was continued for 1 h. The solution was poured onto water, acidified (pH 5–6) by addition of acetic acid, and extracted several times with ether. The combined organic layers were shaken with saturated $NaHCO_3$ solution and further worked up as usual. The remaining oil was chromatographed to provide **7a** (4.99 g, 48%) as an oil and the corresponding $Z$ isomer **8a** (2.36 g, 22%) as a white solid. **7a**: $^1$H NMR $\delta$ 1.1 (9 H, s), 1.1–1.9 (4 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 3.5 (3 H, s), 4.2 (1 H, mc), 4.5 (1 H, mc), 4.9 (1 H, mc), 5.5 (1 H, dd, $J$ = 16 Hz, 6 Hz), 6.4 (1 H, d, $J$ = 16 Hz), 6.9–7.7 (15 H, m); MS $C_{37}H_{42}FNO_3Si$ $m/e$ = 596 (M + 1)$^+$. Anal. ($C_{37}H_{42}FNO_3Si$) C, H, F, N. **8a**: mp 111–113 °C; $^1$H NMR $\delta$ 0.9 (9 H, s), 1.0–1.8 (4 H, m), 2.6 (6 H, s), 3.3 (3 H, s), 4.2 (1 H, mc), 4.3 (1 H, mc), 4.5 (1 H, m), 5.5 (1 H, mc), 6.3 (1 H, d, $J$ = 10 Hz), 6.9–7.8 (15 H, m); MS $C_{37}H_{42}FNO_3Si$ $m/e$ = 596 (M + 1)$^+$. Anal. ($C_{37}H_{42}FNO_3Si$) C, H, F, N.

**(*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]ethenyl]-2-hydroxy-3,4,5,6-tetrahydro-2*H*-pyrans (9a and 10a).** A solution of **7a** (4.93 g, 8.4 mmol) in THF (60 mL), water (60 mL), and acetic acid (100 mL) was refluxed for 48 h. Toluene (150 mL) was added and the resulting mixture was evaporated. The residue was shaken with saturated $NaHCO_3$ solution and worked up as usual. Chromatography (silica gel, cyclohexane/ethyl acetate 1:1) gave **9a** (3.14 g, 63%): mp 119 °C; $^1$H NMR $\delta$ 1.1 (9 H, s), 1.2–2.0 (4 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 3.9–5.0 (3 H, m), 5.1–5.6 (2 H, m), 6.4 (1 H, d, $J$ = 16 Hz), 6.9–7.8 (15 H, m); MS $C_{36}H_{40}FNO_3Si$ $m/e$ = 581 ($M^+$). Anal. ($C_{36}H_{40}FNO_3Si$) C, H, F, N.

The corresponding $Z$ isomer **10a** was prepared by the same procedure in 60% yield: mp 147–149 °C; $^1$H NMR $\delta$ 0.9 (9 H, s), 1.0–1.9 (4 H, m), 2.5 (6 H, s), 4.0–4.4 (2 H, m), 4.8–6.5 (3 H, m), 6.9–7.6 (15 H, m); MS $C_{36}H_{40}FNO_3Si$ $m/e$ = 581 ($M^+$). Anal. ($C_{36}H_{40}FNO_3Si$) C, H, F, N.

**(*E*)- and (*Z*)-4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-6(*S*)-[2-[2,6-dimethyl-4-(4-fluorophenyl)pyridin-3-yl]ethenyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-ones (11a and 12a).** A solution of **9a** (3.00 g, 5.18 mmol), *N*-iodosuccinimide (5.82 g, 25.9 mmol), and tetra-$n$-butylammonium iodide (1.91 g, 5.18 mmol) in dichloromethane (70 mL) was stirred for 2 h at room temperature, poured into a saturated $Na_2S_2O_3$ solution, and worked up in the usual manner. The remaining oil was treated with diisopropyl ether and filtered. After evaporation, the oily residue was chromatographed (silica gel, deactivated with 10% water; cyclohexane/ethyl acetate 1:1) to yield pure **11a** (2.45 g, 76%) as an oil: $^1$H NMR $\delta$ 1.1 (9 H, s), 1.3–1.7 (2 H, m), 2.4–2.6 (8 H, m), 4.2 (1 H, mc), 5.2 (1 H, mc), 5.4 (1 H, mc), 6.5 (1 H, d, $J$ = 16 Hz), 6.9–7.7 (15 H, m); MS $C_{36}H_{38}FNO_3Si$ $m/e$ = 580 (M + 1)$^+$. Anal. ($C_{36}H_{38}FNO_3Si$) C, H, F, N.

In a similar run, the corresponding $Z$ isomer **12a** was obtained from **10a** in 76% yield: mp 188 °C; $^1$H NMR $\delta$ 0.9 (9 H, s), 1.3–1.7 (2 H, m), 2.4 (2 H, mc), 2.6 (6 H, s), 4.2 (1 H, mc), 5.0 (1 H, mc), 5.6 (1 H, mc), 6.5 (1 H, d, $J$ = 11 Hz), 6.9–7.5 (15 H, mc); MS $C_{36}H_{38}FNO_3Si$ $m/e$ = 580 (M + 1)$^+$. Anal. ($C_{36}H_{38}FNO_3Si$) C, H, F, N.

**(*E*)- and (*Z*)-6(*S*)-[2-[2,6-Dimethyl-4-(4-fluorophenyl)-pyridin-3-yl]ethenyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-ones (2a and 3a).** Tetra-$n$-butylammonium fluoride trihydrate (3.42 g, 10.8 mmol) was added to a solution of **11a** (2.10 g, 3.64 mmol) and acetic acid (8.3 mL, 14.5 mmol) in THF (35 mL). The resulting solution was stirred at room temperature for 15 h and then quenched with saturated $NaHCO_3$ solution. After usual workup, the crude product was purified by chromatography (silica gel, desactivated with 10% water; ethyl acetate/methanol 10:1) to give **2a** (0.97 g, 78%) as a white solid: mp 205 °C; $^1$H NMR $\delta$ 1.6–1.9 (3 H, m), 2.5 (3 H, s), 2.6 (3 H, s), 2.6–2.8 (2 H, m), 4.3 (1 H, mc), 5.3 (1 H, mc), 5.5 (1 H, mc), 6.6 (1 H, d, $J$ = 16 Hz), 6.9 (1 H, s), 7.0–7.3 (4 H, m); MS $C_{20}H_{20}FNO_3$ $m/e$ = 341 ($M^+$). Anal. ($C_{20}H_{20}FNO_3$) C, H, F, N.

The corresponding $Z$ isomer **3a** was prepared from **12a** analogously in 75% yield: mp 188 °C; $^1$H NMR $\delta$ 1.5 (1 H, mc), 1.8–2.2 (2 H, m), 2.4–2.6 (8 H, m), 4.2 (1 H, mc), 4.8 (1 H, mc), 5.6 (1 H, mc), 6.5 (1 H, mc), 6.9 (1 H, s), 7.0–7.4 (4 H, m); MS $C_{20}H_{20}FNO_3$ $m/e$ = 341 ($M^+$). Anal. ($C_{20}H_{20}FNO_3$) C, H, F, N.

**6(*R*)-[2-[4-(4-Fluorophenyl)-2-(1-methylethyl)-6-phenylpyridin-3-yl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (4i).** A mixture of **2i** (1.00 g, 2.3 mmol), triethyl amine (50 $\mu$L), methanol (10 mL), and ethyl acetate (10 mL) was shaken under an hydrogen atmosphere, until no more hydrogen was consumed. This mixture was filtered through a pad of Celite and evaporated to give **4i** (0.91 g, 91%) as an oil: $^1$H NMR $\delta$ 1.3–1.8 (11 H, m), 2.3–2.8 (4 H, m), 3.4 (1 H, h, $J$ = 7 Hz), 4.2 (1 H, mc), 4.5 (1 H, mc), 7.1 (2 H, mc), 7.3–7.5 (6 H, mc), 8.1 (2

H, mc); MS $C_{27}H_{28}FNO_3$ $m/e$ = 433 ($M^+$). Anal. ($C_{27}H_{28}FNO_3$) C, H, F, N.

**Biological Assays. HMG-CoA Reductase Inhibition Assay.** The inhibitory activity of compounds **2–4** on rat liver HMG-CoA reductase was estimated with soluble-enzyme preparations obtained from the microsomal fraction.[22] The test was performed according to the method described by Avigan.[23] The complete assay medium contained the following in a total volume of 0.2 mL: Tris, 6mM; EDTA, 2.5 mM; DTT 2.5, mM; NADP, 50 mM; glucose 6-phosphate, 50 mM; glucose 6-phosphate dehydrogenase, 2.8 units; HMG-CoA, 0.91 mM containing 100 nCi (3.7 kBq) of [$^{14}$C] HMG-CoA (New England Nuclear); partially purified enzyme stock solution, 50 μL. Test compounds **2–4** as well as 1b (after conversion to their corresponding potassium 3(*R*),5(*S*)-dihydroxy carboxylates through reaction with 1 equiv of potassium hydroxide in ethanol) were added to the assay system in 10-μL volumes at multiconcentration levels. The complete assay was incubated at 37 °C with shaking during 20 min and the reaction was stopped by addition of 75 μL of 2 N $HClO_4$. After 1 h at room temperature and 10 min in an ice bath, 75 μL of 3 N potassium acetate and 150 μL of water were added, and the precipitate was centrifuged. The supernatant (250 μL) was applicated to an 0.6 × 8.0 cm column containing 100–200-mesh AG 1×8, Cl form (Bio-Rad). Mevalonolactone was eluted with 3.5 mL of Milli-Q water and 0.5-mL portions of the eluate were mixed with 10 mL of Quickscint 212 (Zinsser) for measurement in a Beckman scintillation counter. The assay was carried out in triplicate; the average of six values was calculated for the percentage inhibition. $IC_{50}$ values were obtained by plotting the percentage inhibition against test compound concentration.

**Inhibition of Acetate Incorporation in Cholesterol in Cultures of HEP G2 Cells.** Monolayers of HEP G2 cells in RPMI 1640 medium (Flow) with 10% delipidated fetal calf serum were preincubated for 1 h with suitable concentrations of the test compounds **2**, **3**, or **4**. After addition of $^{14}$C-labeled sodium acetate, the incubation was continued for 3 h. [$^3$H] Cholesterol was added as an internal standard and an aliquot of the cells was saponified with alkali. The lipids were extracted with chloroform/methanol 2:1. After addition of carrier cholesterol, the lipid mixture was separated preparatively on TLC plates using chloroform/acetone 9:1. The cholesterol zone was visualized with iodine vapor and a TLC radioscanner and scraped out. The amount of [$^{14}$C] cholesterol was determined scintigraphically. With another aliquot of cell monolayers, cell proteins were determined for calculation of [$^{14}$C] cholesterol biosynthesis per milligram of cell protein. The same procedure was done at three different inhibitor concentrations, using cells of the same culture, and additionally without preincubation with a test compound (solvent control).

For each compound, $IC_{50}$ values were calculated by plotting the ratio between the relative amount of [$^{14}$C] cholesterol synthesized in inhibitor-treated cells and in solvent controls against inhibitor concentrations. Relative potencies were calculated on the basis of 1b as external standard.

**Hypocholesterolemic Activity in Rabbits.** Normolipemic male white New Zealand rabbits (3–5.5 kg) in groups of four to six animals received the compounds, suspended in 1% aqueous (carboxymethyl)cellulose (Tylose) daily in the morning by stomach tube; the control groups were given only Tylose. In samples of venous blood, taken every 3–4 days 20 h after the oral administration, serum total cholesterol was enzymatically determined by test combination of Boehringer-Mannheim (CHOD-PAP high-performance method). The serum cholesterol level of drug-treated groups was compared with that of control groups. After the time of "administration" a time of "withdrawal" followed.

**Conformational Analysis and Structural Comparison of Compounds 1b and 2i.** A computer-assisted conformational analysis of 1b and **2i** was carried out using a commercially available program[24] in order to determine their low-energy conformations.

An initial conformation of **1b** was modeled from the conformation of compactin (**1a**) as determined by X-ray crystallography.[25,26] A systematic conformational search with rotatable bonds

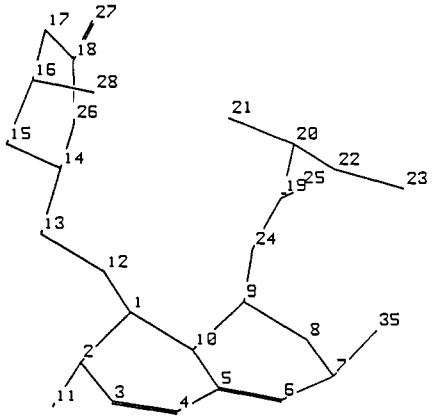



**Figure 3.** Low-energy conformation of 1b as determined by computer-assisted analysis (hydrogen atoms omitted).

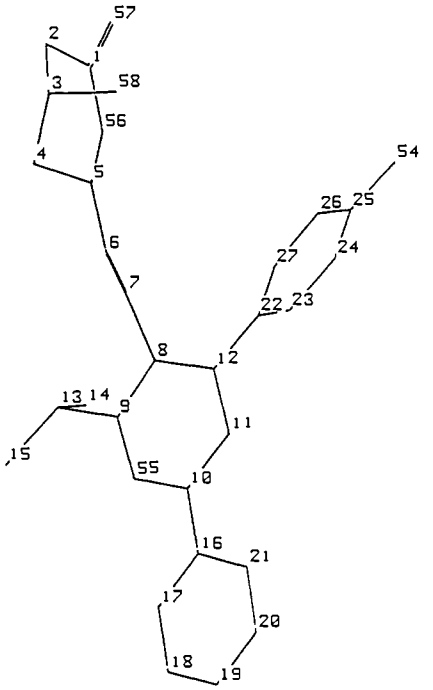



**Figure 4.** Low-energy conformation of **2i** as determined by computer-assisted analysis (hydrogen atoms omitted).

13–14, 12–13, 1–12, 9–24, 19–24, 19–20, and 20–22 (see Figure 3) being varied in 30° steps over a range of 360° led to 13669 conformations. Atom number 14 was the anchor atom. Scale factors for the van der Waals radii of 0.85 for 1,5 and greater interactions, 0.75 for 1,4 interactions, and 0.55 for H-bond interactions were specified in order to make sure that the initial conformation was contained in the set of generated conformations. A set of 1605 conformations were within 5.0 kcal/mol of the energy minimum. The minimum was located at the starting conformation with an energy of −9.8 kcal/mol (Figure 3). All energy values did not include Coulombic interactions.

A systematic conformational search was carried out in order to also determine the low-energy conformations of **2i**. The initial conformation was taken from the crystal structure (see Figure 2). Since there are two conformations present in the crystal, the one which has the lactone in almost the same conformation as **1b** (conformer B) was chosen. The energy of this conformation could be minimized[24] from 262.7 to 5.0 kcal/mol. Although the

(22) Philippi, B. W.; Shapiro, D. J. *J. Lipid Res.* **1979**, *20*, 588.
(23) Avigan, J.; Bathena, S. J.; Schreiner, M. E. *J. Lipid Res.* **1975**, *16*, 151.
(24) SYBYL 3.3, Tripos Associates, St. Louis, MI 63117.
(25) Brown, A. G.; Smale, T. C. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1165.
(26) Since the crystal structure of **1b** is not known, 1a was used for analysis. Compactin differs from 1b by just one methyl group, suggesting that the conformational energies of both compounds should be similar.

energy decreased substantially, the original and minimized structure showed a standard deviation of only 0.15 Å. The high energy of the crystal structure is due to terminal hydrogens being slightly displaced. The systematic conformational search[24] yielded 1056 conformations. The rotatable bonds 5–6, 6–7, 7–8, 12–22, 10–16, and 9–13 (see Figure 4) were varied in steps of 30°, 180°, 30°, 30°, and 30° over ranges of 360°, 360°, 360°, 180°, 180°, and 360°, respectively. Atom number 5 was chosen to be the anchor atom. The van der Waals radii were scaled by 0.9 for 1,5 and greater interactions, 0.8 for 1,4 interactions, and 0.6 for H-bond interactions. With these scale factors the initial conformation was contained in the set of generated conformations.

From the 1056 conformations generated, 348 were within 5.0 kcal/mol of the minimum of 3.5 kcal/mol found. The energies did not contain Coulombic interactions. With use of computer graphics, these conformations were oriented in space such that the lactone moiety approximately fitted the lactone of 1b and the fluorophenyl group qualitatively matched the ester group of 1b. The structure of **2i** thus selected was then subjected to a flexible fit[24] against 1b.

The conformation of **2i** chosen graphically differs from its crystal structure. However, with an energy value of 4.0 kcal/mol, it still is one of the low-energy conformations. For the flexible fit a force constant of 100.0 kcal/mol Å$^2$ was specified among the oxygen atoms 56, 57, and 58 of **2i** and 26, 27, and 28 of 1b. A force constant of 20.0 kcal/mol Å$^2$ was given for atom pairs 8 and 27 of **2i** and 1 and 24 of 1b. The fit energy of 16.0 kcal/mol was counterbalanced by an energy of 17.4 kcal/mol of **2i**. The standard deviation of the specified atoms was calculated to be 0.217 Å. When the fitted structure was relaxed, its energy is lowered to 8.1 kcal/mol, which appeared to be mainly due to releasing angle strain. The structure underwent only slight changes as indicated by standard deviation of atoms of 0.066 Å.

**X-ray Structural Analysis of 2i.** Compound **2i** (60 mg) was recrystallized from a mixture of 1 mL of diisopropyl ether and 0.5 mL of ethyl acetate. The crystal used for X-ray analysis was 0.55 × 0.35 × 0.13 mm, sealed in a Lindeman glass capillary: 25 reflections for cell refinement, Mo-K$\alpha$ radiation, Nicolet R3 computer-controlled diffractometer, monoclinic, $C2$, $Z = 8$, $a = 34.99$ (2) Å, $b = 8.201$ (4) Å, $c = 16.66$ (1) Å, $\beta = 104.98$ (3)°, $V = 4618.2$ Å$^3$, $D = 1.241$ g/cm$^3$, $\mu = 0.8$ mm$^{-1}$, $\Omega$ scan, $2\vartheta_{max} = 56°$, 3° $\vartheta$/min, 1 standard reflection (8 0 0), variation 2.8%; 6421 reflections measured, 4616 of the 5942 unique reflections had $I > \sigma(I)$ and were used for the structure analysis, $-46 < h < 2$, $0 < k < 10$, $-21 < l < 21$, no corrections for absorption or extinction. The phase problem could not be solved by the usual direct methods, but it was solved by the random-start multisolution program SHELXS-86;[27] in the final refinement all hydrogens were also refined, partly found in a difference electron density synthesis and partly calculated by using a model with idealized geometry (C–H 0.96 Å); other atoms were refined anisotropically; least-squares refinement on $F$ with 4609 data, 720 parameters: $w = 1/\sigma(F)$, $R(1) = 0.108$, $R(2) = R(w) = 0.045$, $S = 1.7$ max $\Delta/\sigma = 0.1$; 10 largest peaks in final difference electron density synthesis between 0.27 and 0.31 $e$ Å$^{-3}$; calculations were performed with a Nova 3/12 computer and SHELXTL scattering factors and $f'$, $f''$ from *International Tables for X-ray Crystallography* (1974).

**Supplementary Material Available:** Analytical and spectral data for compounds **2a–w**, **3a,c,r**, and **4d,i,r** and analysis data for **6a–w** and **20a–w** (10 pages). Ordering information is given on any current masthead page.

(27) Sheldrick, G. M. In *Crystallographic Computing 3*, Sheldrick, G. M., Krueger, C., Goddard, R., Eds.; Oxford University Press, 1985; p 175.